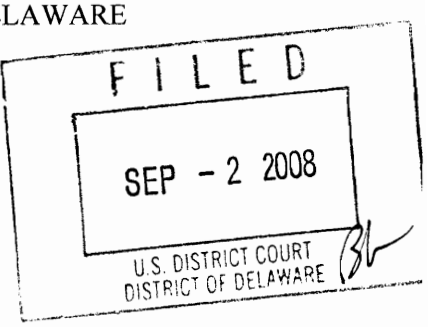
IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DELAWARE



DAVID W. RUSH,)
Plaintiff,)
v.) C.A. 07-514-SLR
CORRECTIONAL MEDICAL SERVICES, Inc, et al,)
Defendants.

PLAINTIFF'S MOTION FOR JUDICIAL NOTICE

Comes now, Rush, a pro se plaintiff, pursuant to F.R.E., Rule 201 and requests the Court to take judicial notice of medical facts that are subject to ready verification, not subject to reasonable question, and are supported or verified herein via valid medical authority or diagnosis. Rush is pro se and he seeks pleading leniency under *Haines v. Kerner*, 404 U.S. 519 (1972). Rush offers the following:

"Rule 201 of the F.R.E. requires the court to take judicial notice of facts capable of accurate and ready determination by resort to sources whose accuracy cannot be reasonably questioned when a party requests that it do so and supplies the necessary information. F.R.E. 201 (b), (d)." See *U.S. v. Isaac*, 134 F.3d 199, 206 (3rd Cir. 1998).

Rush seeks judicial notice of the following medical facts because these facts are capable of accurate and ready determination by resort to accepted and non-controversial sources whose accuracy cannot be reasonably questioned and Rush supplies said necessary information herein:

I. The Mayo Foundation for Medical Education and Research establishes the following medical facts:

1. Late stage symptoms of Hepatitis C ("HCV") include the following symptoms:

a. Fatigue,

b. Lack of appetite,

c. Nausea and vomiting,

d. Jaundice,

e. Low-grade fever. (See Attachment A Medical Article by Mayo Clinic, p. 2 of 8; accessed on 08-11-2008 at http: // www.mayoclinic. Com/print/hepatitis-c).

2. Aggravated or High Risk Symptoms of HCV that mandate immediate medical attention are as follows:

a. Increased drowsiness, mental confusion or irritability,

b. Vomiting, diarrhea or abdominal pain,

c. Increased jaundice,

d. Fever, and

e. Loss of appetite. (See Attachment A at p. 3 of 8).

3. Treatment is recommended for HCV patients who experience the following:

a. A positive test result indicating hepatitis C virus circulating in the bloodstream,

b. A liver biopsy that indicates significant liver damage, and

c. Elevated levels of a liver enzyme called alanine aminotransferase (ALT) in the blood.

(See Attachment A at p. 4 of 8).

4. The standard of care for Hepatitis C treatment is weekly injections of pegylated interferon alfa combined with twice daily oral doses of ribavirin. (i.e. antiviral therapy-Interferon/Ribavirin).

(See Attachment A at p. 5 of 8).

5. Side effects of Interferon therapy include the following:

a. Severe flu-like symptoms,

b. Irritability,

c. Depression,

e. Concentration and memory problems,

f. Fatigue, and

g. Insomnia. (See Attachment A at p. 5 & 6 of 8).

6. Side effects of Combination Interferon/Ribavirin therapy include the following:

a. Psychosis or suicidal behavior. (See Attachment A at p. 6 of 8).

II. The Physician's Desk Reference, PDR Ed. 62, 2008 establishes the following medical facts:

1. Based on clinical trials that:

a. Ribavirin monotherapy (i.e. alone without Interferon) is not effective for the treatment of chronic hepatitis C virus infection: therefore, Ribavirin Capsules *must not be used alone.* The *safety and efficacy* of Ribavirin Capsules have only been established when used together with Interferon, and

b. Also, establishes significant adverse side effects including sever depression and suicidal ideation, etc.

(See Attachment B Physician's Desk Reference, PDR Ed. 62, 2008, Thompson Healthcare Inc., NJ 2007, p. 3 at "Warnings").

III. Roche Pharmaceutical Manufacturer's Product Information regarding Interferon (i.e. Pegasys) and Ribavirin (i.e. Copegus) establishes the following medical facts:

1. Most common or aggravated side effects of Pegasys or Copegus are the following:

a. Depression and suicide,

b. Psychosis,

c. Aggression,

e. Anxiety,

f. Hypothyroidism,

g. Psychotic disorders and hallucination among other serious side effects.

(See Attachment C Excerpt from Roche's Product Information for Pegasys, p. 1 & 2).

IV. The Mayo Foundation for Medical Education and Research establishes the following medical facts:

1. Risk factors for developing Liver Cancer are the following:
    a. Chronic infection with Hepatitis C virus is by far the most important risk factor for liver cancer,
    b. Cirrhosis, which is a progressive and irreversible condition that causes scar tissue to form in the liver, increases the risks of developing liver cancer.

(See Attachment D Medical Article by Mayo Clinic, p. 3 of 12; accessed on 08-11-2008 at http: // www.mayoclinic. Com/print/hepatitis-c).

V. The Mayo Foundation for Medical Education and Research establishes the following medical facts:

1. The thyroid gland is a small, butterfly-like shaped gland located at the base of the front of the neck, just below the Adam's apple. Hormones produced by the thyroid gland have an *enormous* impact on one's health, *affecting all aspects of the metabolism.* (See Attachment E Medical Article by Mayo Clinic, p. 3 of 9; accessed on 08-11-2008 at http: // www.mayoclinic.Com/print/hypothyroidism/DS00353/method).).

2. The thyroid gland produces hormones that maintain the following important bodily functions:
    a. The rate at which the body uses fat and carbohydrates,
    b. Controls body temperature, and
    c. Regulates heart rate and production of protein.

(See Attachment E Medical Article by Mayo Clinic, p. 3 of 9; accessed on 08-11-2008 at http: // www.mayoclinic.Com/print/hypothyroidism/DS00353/method).

3. Symptoms of Hypothyroidism include the following:
    a. Fatigue or sluggishness,
    b. Increased sensitivity to cold,
    c. Constipation,
    d. Pale, dry skin,
    e. A puffy face (i.e. edema known as phantom allergies),
    f. Elevated blood cholesterol level,
    g. Weight gain,
    h. Muscle aches, tenderness and stiffness,
    i. Pain, stiffness or swelling in the joints,
    j. Muscle weakness, and
    k. Depression.

(See Attachment E Medical Article by Mayo Clinic, p. 2 of 9; accessed on 08-11-2008 at http: // www.mayoclinic. Com/print/hypothyroidism/DS00353/method).

VI. The Thyroid Foundation of America establishes the following medical facts:

1. Hypothyroidism is associated with an increased risk of atherosclerosis and heart disease.

(See Attachment F The Thyroid Foundation of America, p. 1 of 1; accessed on 09-27-2007 at http://www.tsh.org/askthedoctor/homocysteine.html).

2. Even slight changes in Thyroid Stimulating Hormone ("TSH") level could signify a serious health risk and a change in thyroid prescription may change the TSH and pose serious health risks.

(See Attachment G The Thyroid Foundation of America, p. 1 of 2; accessed on 09-27-2007 at http://www.tsh.org/disorders/treatments/changingmeds.html).

VII. The American Association of Clinical Endocrinologists establishes the following medical facts:

1. Hypothyroidism is treated with a single daily dose of Levothyroxine and because the thyroid hormone acts slowly in the body, *it may take several months after treatment is started to notice improvement in symptoms*.
2. Most cases of hypothyroidism are permanent and often progressive, so it is necessary to treat the condition throughout one's lifetime.
3. Since the body is sensitive to even small changes in thyroid hormone, it is essential to comply with the following medication administration:
    a. Maintain optimal adjustment of thyroid hormone,
    b. Take medication in consistent manner daily,
    c. Take medication at the same time every day, and
    d. Take the same brand of medication.

    (See Attachment H American Association of Clinical Endocrinologists, p. 1 of 2 and 3 or 4; accessed on 09-27-2007 at http://www. medem.com/search/article.html).

VIII. The Eleventh Circuit Court of Appeals took judicial notice of the following substantially similar medical facts:

1. Disorders of the thyroid gland fit squarely within the meaning of "impairment"… "It is common knowledge that the thyroid gland is an integral part of the endocrine system, as can be verified by turning to an ordinary dictionary. See e.g. Random House Unabridged Dictionary 1980 (Stuart B. Flexner & Leonore C. Hauck eds., 2d ed. 1993) (defining the thyroid gland as "a two=lobed endocrine gland…that secretes two hormones that regulate the rates of metabolism, growth, and development") See *Harris v. H & W Contracting, Co.*, 102 F.3d 516 at 520 (11th Cir 1996).
2. In addition, the Harris Court accepted the following medical facts:
    "We take judicial notice the 'Graves disease consists of hyperthyroidism' and it 'is capable of substantially limiting major life activities if left untreated by medication," as established by The Merck Manual of Diagnosis and Therapy (Robert Berkow, et al. eds, 15th ed 1987) (ID at 102 F.3d 522).

Accordingly, the medical facts supplied above –and the Circuit Court's judicial notice of substantially similar endocrine/hormone system disease and medications- regarding the thyroid gland (i.e. endocrine system), hypothyroidism, and treatment of the condition by medication establish the aforementioned medical facts as they are capable of ready determination, not subject to reasonable questions, and thus F.R.E. Rule 201 warrants judicial notice of them. Specifically the following:

i. The thyroid gland is an integral part of the endocrine system that regulates the rates of metabolism, growth, and development, heart rate, and fat and carbohydrate use;

ii. Hypothyroidism is a progressive and usually life=long disease in which the thyroid gland fails to produce said essential hormones and this condition is associated with serious symptoms (i.e. depression, fatigue, increase in cholesterol and incidence of atherosclerosis and heart disease), and substantial impairment of daily life activities;

iii. Hypothyroidism is treated by a single daily dose of thyroid hormone (i.e. Levothyroxine) and it is essential to consistently administer said medication because even small changes in the TSH may pose serious health risks; and

iv. Hypothyroidism is capable of substantially impairing or limiting major life activities if left untreated by medication.

IX. The treating Infectious Disease Physician, Doctor McDonald, has verified/diagnosed Rush as experiencing the following acute symptoms of Chronic Hepatitis C/Hypothyroidism and/or side effects of HCV therapy (i.e. Interferon/Ribavirin):

a. Significant mental confusion or cognitive impairment,
b. Significant Insomnia,
c. Acute depression,
d. Significant fatigue,
e. Acute irritation,
f. Mood and behavioral problems,
g. Acute flu-like symptoms and upset stomach.

(See Attachment 1 Medical Verification from Doctor McDonald).

Accordingly, the Court is also warranted in taking judicial notice of the medical facts regarding HCV, Liver Cancer, and HCV therapy –its side effects and warnings- listed above at items I through IV; and judicial notice that Rush has been diagnosed with Chronic HCV, is currently undergoing 48 weeks of HCV therapy, and diagnosed with hypothyroidism; and that Rush's treating physician has verified Rush as experiencing the aggravated symptoms/side effects listed above at item IX and that these disease and/or treatments have and do cause Rush to experience significant impairment of his daily normal activities and cognitive faculties. Lastly, that said side-effects are likely to last until six months after the 48 weeks of HCV therapy is completed.

WHEREFORE, Rush requests the Court to take judicial notice of the above listed and supported medical facts at items I. through IX. as warranted.

Respectfully,

David Rush

David Rush
1181 Paddock Rd., Smyrna, DE 19977

8/26/08
Date

Attachment A

Certificate of Service

I, David Rush, hereby certify that I have served a true And correct cop(ies) of the attached: PLAINTIFF'S MOTION FOR JUDICIAL NOTICE upon the following parties/person (s):

TO:

James E. Drnec, Esq.
(Counsel for CMS, et al)
711 King St.
Wilmington, DE 19801

TO:

TO:

TO:

BY PLACING SAME IN A SEALED ENVELOPE, and depositing same in the United States Mail at the Delaware Correctional Center, Smyrna, DE 19977.

On this 29th day of August, 2008

David Rush

MayoClinic.com
Tools for healthier lives

Original Article:http://www.mayoclinic.com/health/hepatitis-c/DS00097

Hepatitis C

Definition

Hepatitis C is a virus that often silently attacks your liver. Most people infected with the hepatitis C virus (HCV) have no symptoms at all. In fact, most people don't know they have the disease until liver damage shows up, decades later, during routine medical tests.

Hepatitis C is one of six identified hepatitis viruses — the others are A, B, D, E and G. All cause the liver to become inflamed, which interferes with its ability to function. Hepatitis C is generally considered to be among the most serious of these viruses.

Over time, if you have a hepatitis C infection, it can lead to liver cancer, liver failure or cirrhosis — irreversible and potentially fatal scarring of the liver. Unlike HIV, the virus that causes AIDS, the hepatitis C virus usually isn't transmitted through sexual contact. Instead, you're more at risk if you're exposed to contaminated blood — through needles shared during drug use or through blood transfusions.

Although vaccines exist for hepatitis A and B, no vaccine for hepatitis C has been developed. Researchers hope to find a medication that will slow or stop the growth of the virus and prevent long-term complications, such as cirrhosis and cancer, from developing.

Symptoms

Early-stage signs and symptoms

Commonly, hepatitis C infection produces no signs or symptoms during its earliest stages. When it does, they're generally mild and flu-like and may include:

- Slight fatigue
- Nausea or poor appetite
- Muscle and joint pains
- Tenderness in the area of your liver

Later stage signs and symptoms
Even if you develop chronic hepatitis from the hepatitis C virus, you may have few, if any, symptoms. In many cases, signs and symptoms may not appear for decades. Sometimes, though, you may experience one or more of the following:

- Fatigue
- Lack of appetite
- Nausea and vomiting
- Persistent or recurring yellowing of your skin and eyes (jaundice)
- Low-grade fever

Hepatitis C can cause damage to your liver, even if you don't have symptoms. You're also able to pass the virus to others without having any symptoms yourself. That's why it's important to be tested if you think you've been exposed to hepatitis C or if you engage in behavior that puts you at risk.

Causes

In general, you get hepatitis C by coming in contact with blood contaminated with the virus. Most people with hepatitis C became infected through blood transfusions received before 1992, the year improved blood-screening tests became available.

You can also get the virus by injecting drugs with contaminated needles and, less commonly, from contaminated needles used in tattooing and body piercing. Needle exchange programs, which increase the availability of sterile needles, are helping to reduce the risk of hepatitis C, HIV and other blood-borne diseases.

A small number of babies born to mothers with hepatitis C acquire the infection during childbirth. Mother-to-infant transmission rates are higher among women infected with both hepatitis C and HIV. Talk with your doctor about these risks before becoming pregnant.

In rare cases, hepatitis C may be transmitted sexually. And in many people infected with hepatitis C, no risk factor can be identified.

Risk factors

Effective blood-screening procedures have greatly reduced the chances of hepatitis C infection from transfusions. But if you received a blood

transfusion before 1992, you're at risk of hepatitis C.

You are also at risk if you:

- Have used illicit intravenous (IV) or intranasal drugs, such as cocaine
- Received an organ transplant before 1992
- Are a health care worker who has been exposed to infected blood
- Received clotting factor concentrates before 1987 or have the clotting disease hemophilia and received blood before 1992
- Are receiving hemodialysis for kidney failure
- Were born to a woman with a hepatitis C infection

When to seek medical advice

See your doctor if you think you may have been exposed to the hepatitis C virus, if you notice your skin or eyes turning yellow or if you have any other symptoms of hepatitis. Don't let your concern about what others may think keep you from getting medical care.

If you received a blood transfusion before 1992 from a donor who later tested positive for the hepatitis C virus, you may have received a letter from your hospital or blood bank recommending testing.

If you're being treated for hepatitis, see your doctor right away if you develop any of the following signs and symptoms:

- Increased drowsiness, confusion or irritability
- Vomiting, diarrhea or abdominal pain
- Increased jaundice
- Skin rash
- Fever
- Loss of appetite

Tests and diagnosis

A blood test can determine whether you have the hepatitis C virus. If test results indicate that you have HCV, your doctor may measure the quantity of the virus in your blood (viral load) and evaluate the genetic makeup of the virus (genotype). There are six known HCV genotypes. Knowing which genotype you have will help your doctor determine the best course of treatment for you and how likely you are to respond to treatment.

Your doctor may also recommend a liver biopsy, a procedure in which a small sample of liver tissue is removed for microscopic analysis. Before the biopsy, you'll receive a local anesthetic to decrease the pain. Your doctor then inserts a thin needle into your liver to remove the tissue sample. Liver biopsy is unlikely to have any complications, although you

may have some pain or bleeding afterward. One in 100 to one in 1,000 people may experience significant bleeding.

Although a biopsy isn't necessary to confirm a diagnosis of hepatitis C, it can help determine the severity of the disease and guide treatment decisions. It may also help rule out other causes for your liver problem, such as alcoholic or drug-induced hepatitis, autoimmune hepatitis or excess iron (hereditary hemochromatosis).

Complications

CLICK TO ENLARGE


Normal liver and liver with cirrhosis

A small number of people infected with hepatitis C fight off the virus on their own without any permanent damage. For the rest, the disease settles in and slowly attacks the liver, although even then, the course of the disease can vary greatly from person to person.

Most people infected with HCV develop chronic hepatitis. Some people infected witfh hepatitis C develop cirrhosis, usually within 20 to 30 years after infection. This risk is higher and the progression is faster if you also have HIV infection. Of those who develop cirrhosis, the risk of developing liver failure is about 4 percent a year. In addition, between 1 percent and 5 percent of people with HCV eventually develop liver cancer.

HCV also may increase the risk of developing several types of lymphatic system cancers (lymphomas). Your risk of non-Hodgkin's lymphoma, for example, may increase by 20 percent to 30 percent. Rarely, HCV infection can be associated with skin and kidney problems. The hepatitis C virus is linked to an increased risk of porphyria cutanea tarda, a condition that may cause a blistering rash, to cryoglobulinemia, which can cause a purplish rash (purpura) on your lower extremities, and may cause kidney damage.

Treatments and drugs

A diagnosis of HCV doesn't necessarily mean you need treatment.

You may need treatment if
The National Institutes of Health recommends treatment for HCV if you have:

- A positive test result indicating hepatitis C virus circulating in your bloodstream
- A biopsy that indicates significant liver damage
- Elevated levels of a liver enzyme called alanine aminotransferase (ALT) in your blood

You may not need treatment if
If you have only slight liver abnormalities, your doctor may decide against medical treatment because your long-term risk of developing a serious disease is slight, and the side effects of treatment can be severe.

On the other hand, because there's no foolproof way to know whether you'll develop liver disease later on, your doctor may recommend fighting the virus. Improved treatment methods and a higher success rate in fighting hepatitis sometimes tip the balance in favor of more aggressive approaches.

Drug therapies — pegylated interferon alfa and ribavirin
The standard of care for hepatitis C treatment is weekly injections of a drug called pegylated interferon alfa combined with twice-daily oral doses of ribavirin (Rebetol) — a broad-spectrum antiviral agent. Two pegylated interferon medications are available, peginterferon alfa-2b (Peg-Intron) and peginterferon alfa-2a (Pegasys).

The goal of HCV treatment is to clear the virus from your bloodstream. Combined pegylated interferon and ribavirin clear HCV infection in 40 percent to 80 percent of those treated. It's success often depends on the type of infection. For example, this treatment clears infection in up to half the people with genotype 1 — the most common genotype found in the United States — and in up to 80 percent of those with genotypes 2 and 3.

Duration of treatment
If you have genotype 1 HCV, your doctor may recommend a course of relatively high-dose medications for 48 weeks. If you have genotype 2 or genotype 3, a 24-week course of medications at a lower dose may be adequate.

If one course of combined pegylated interferon and ribavirin doesn't clear HCV from your bloodstream, your doctor may recommend a second course of combination therapy. If your viral load declined during the first round of medications, a second round may clear the virus completely. Even if there was no change in your viral load during the first course of treatment, a second course may help reduce the damage HCV does to your liver.

Side effects of medications
Interferon side effects include severe flu-like symptoms, irritability, depression, concentration and memory problems, skin irritation, fatigue

and insomnia.

Ribavirin can cause a low red blood cell count (anemia), itchiness, nasal congestion, skin irritation, fatigue and birth defects.

Combination therapy including pegylated interferon and ribavirin may cause psychosis or suicidal behavior in a small number of people. For this reason, treatment with interferon isn't recommended if you have a history of uncontrolled major depression. You're also not a good candidate for this treatment if you're pregnant or have untreated thyroid disease, low blood cell counts or autoimmune disease, or if you drink alcohol or use drugs and are unwilling to stop or seek help with stopping.

Side effects from combined pegylated interferon and ribavirin are generally most severe during the first few weeks of treatment, and may be improved with pain relief medications and antidepressants. However, some people taking interferon need their dosage reduced because of severe side effects, and others must stop treatment.

Liver transplantation

The best treatment for people with end-stage liver disease is liver transplantation. However, the number of people awaiting transplants far exceeds the number of donated organs. But several new developments in transplantation may make it possible for more people to receive transplants.

These developments include the donation of liver segments from living relatives, splitting one donated liver between two recipients, new organ allocation policies and, especially, new approaches to liver transplants for people with HCV.

Until recently, HCV-infected livers were routinely discarded. But studies show that people already infected with HCV who receive livers from HCV-positive donors can do as well as if they had received a liver not infected with the virus. This may mean that many more livers will become available for people with hepatitis C.

Liver transplantation does not cure HCV. The majority of people with hepatitis C who receive liver transplants experience a recurrence of the virus. Those with HCV who receive liver transplants also are at accelerated risk of developing cirrhosis within five years. Treatment with HCV-fighting medications may help prevent a recurrence of infection or treat recurrent illness that develops after a liver transplant. However, the effectiveness of this type of treatment after a liver transplant is unclear.

Immunizations

Your doctor will likely recommend that you are vaccinated against the hepatitis A and B viruses. These are separate viruses that can also cause

liver damage and complicate treatment of hepatitis C.

Prevention

Because no effective vaccine for hepatitis C exists, the only way to protect yourself is to avoid becoming infected. That means taking the following precautions:

- **Avoid illegal drug use.** Don't share needles or other drug paraphernalia. Contaminated drug paraphernalia is responsible for more than half of all new hepatitis C cases. Avoid nasal use of cocaine. Blood on shared straws also can transmit the virus.
- **Avoid body piercing and tattooing.** If you do undergo piercing or tattooing, be absolutely certain the equipment is sterile.
- **Avoid risky sexual behavior.** Don't engage in unprotected sex with multiple partners or with one partner whose health status is uncertain. Sexual transmission between monogamous couples may occur, but the risk is low.

Lifestyle and home remedies

If you receive a diagnosis of hepatitis C, your doctor will likely recommend certain lifestyle changes. These measures will help keep you healthy longer and protect the health of others as well:

- **Eliminate alcohol consumption.** Alcohol speeds the progression of liver disease.
- **Avoid medications that may cause liver damage.** Your doctor can advise you about these medications, which may include some over-the-counter (OTC) medications, such as acetaminophen (Tylenol, others), as well as prescription drugs.
- **Maintain a healthy lifestyle.** Be sure you exercise regularly, get plenty of rest and eat a healthy diet that emphasizes fresh fruits, vegetables and whole grains.
- **Help prevent others from coming in contact with your blood.** Cover any wounds you may have and don't share razors or toothbrushes. Don't donate blood, body organs or semen, and advise health care workers that you have the virus.

Alternative medicine

In Europe, the herb milk thistle (Silybum marianum) has been used for centuries to treat jaundice and other liver disorders. Today, scientific studies have confirmed that the chief constituent of milk thistle, silymarin,

may aid in healing and rebuilding the liver. Silymarin seems to stimulate the production of antioxidant enzymes that help the liver neutralize toxins. It also may decrease inflammation in the liver. However, more study is needed. Although milk thistle may help the liver, it won't cure hepatitis, and it won't protect you from contracting the virus.

Milk thistle is available in capsules or alcohol-free extracts. Check with your doctor before trying this or any other herb, to make sure it won't interact with other medications you're taking.

By Mayo Clinic Staff
Sept. 14, 2007

DS00097

Attachment B

PDR® 62 EDITION 2008

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ISBN: 1-56363-660-3

TABLE 9. Guidelines for Dose Modifications

	Dose Reduction* REBETOL – Adults: 600 mg daily Pediatrics: half the dose INTRON A – Adults: 1.5 million IU TIW Pediatrics: 1.5 million IU/m² TIW	Permanent Discontinuation of Treatment REBETOL and INTRON A
Hemoglobin	<10 g/dL (REBETOL) **Cardiac History Patients Only. ≥2 g/dL decrease during any 4-week period during treatment (REBETOL/INTRON A)**	<8.5 g/dL **Cardiac History Patients Only. <12 g/dL after 4 weeks of dose reduction**
White blood count	$<1.5 \times 10^9$/L (INTRON A)	$<1.0 \times 10^9$/L
Neutrophil count	$<0.75 \times 10^9$/L (INTRON A)	$<0.5 \times 10^9$/L
Platelet count	Adults: $<50 \times 10^9$/L (INTRON A) Pediatrics: $<80 \times 10^9$/L (INTRON A)	Adults: $<25 \times 10^9$/L Pediatrics: $<50 \times 10^9$/L

*Study medication to be dose reduced is shown in parenthesis.

Vial/Pen Label Strength	Fill Volume	Concentration
3 million IU vial	0.5 mL	3 million IU/0.5 mL
18 million IU multidose vial†	3.8 mL	3 million IU/0.5 mL
18 million IU multidose pen††	1.5 mL	3 million IU/0.2 mL

† This is a multidose vial which contains a total of 22.8 million IU of interferon alfa-2b, recombinant per 3.8 mL in order to provide the delivery of six 0.5-mL doses, each containing 3 million IU of interferon alfa-2b, recombinant (for a label strength of 18 million IU).

†† This is a multidose pen which contains a total of 22.5 million IU of interferon alfa-2b, recombinant per 1.5 mL in order to provide the delivery of six 0.2-mL doses, each containing 3 million IU of interferon alfa-2b, recombinant (for a label strength of 18 million IU).

	Each REBETRON Combination Package Consists of:	
For Patients ≤75 kg	A box containing 6 vials of INTRON A Injection (3 million IU in 0.5 mL per vial), 6 B-D Safety-Lok™ syringes with a safety sleeve, alcohol swabs, and one bottle containing 70 REBETOL Capsules.	(NDC 0085-1241-02)
	One 18 million IU multidose vial of INTRON A Injection (22.8 million IU per 3.8 mL; 3 million IU/0.5 mL), 6 B-D Safety Lok™ syringes with a safety sleeve, alcohol swabs, and one bottle containing 70 REBETOL Capsules.	(NDC 0085-1236-02)
	One 18 million IU INTRON A Injection multidose pen (22.5 million IU per 1.5 mL; 3 million IU/0.2 mL), 6 disposable needles, alcohol swabs, and one bottle containing 70 REBETOL Capsules.	(NDC 0085-1258-02)
For Patients >75 kg	A box containing 6 vials of INTRON A Injection (3 million IU in 0.5 mL per vial), 6 B-D Safety-Lok™ syringes with a safety sleeve, alcohol swabs, and one bottle containing 84 REBETOL Capsules.	(NDC 0085-1241-01)
	One 18 million IU multidose vial of INTRON A Injection (22.8 million IU per 3.8 mL; 3 million IU/0.5 mL), 6 B-D Safety Lok™ syringes with a safety sleeve, alcohol swabs, and one bottle containing 84 REBETOL Capsules.	(NDC 0085-1236-01)
	One 18 million IU INTRON A Injection multidose pen (22.5 million IU per 1.5 mL; 3 million IU/0.2 mL), 6 disposable needles, alcohol swabs, and one bottle containing 84 REBETOL Capsules.	(NDC 0085-1258-01)
For REBETOL Dose Reduction	A box containing 6 vials of INTRON A Injection (3 million IU in 0.5 mL per vial), 6 B-D Safety-Lok™ syringes with a safety sleeve, alcohol swabs, and one bottle containing 42 REBETOL Capsules.	(NDC 0085-1241-03)
	One 18 million IU multidose vial of INTRON A Injection (22.8 million IU per 3.8 mL; 3 million IU/0.5 mL), 6 B-D Safety Lok™ syringes with a safety sleeve, alcohol swabs, and one bottle containing 42 REBETOL Capsules.	(NDC 0085-1236-03)
	One 18 million IU INTRON A Injection multidose pen (22.5 million IU per 1.5 mL; 3 million IU/0.2 mL), 6 disposable needles, alcohol swabs, and one bottle containing 42 REBETOL Capsules.	(NDC 0085-1258-03)

actions or laboratory abnormalities develop during combination REBETOL/INTRON A therapy, the dose should be modified, or discontinued if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, REBETOL/INTRON A therapy should be discontinued.

REBETOL/INTRON A therapy should be administered with caution to patients with pre-existing cardiac disease. Patients should be assessed before commencement of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be stopped. (See **WARNINGS**.)

For patients with a history of stable cardiovascular disease, a permanent dose reduction is required if the hemoglobin decreases by ≥2 g/dL during any 4-week period. In addition, for these cardiac history patients, if the hemoglobin remains <12 g/dL after 4 weeks on a reduced dose, the patient should discontinue combination REBETOL/INTRON A therapy.

It is recommended that a patient whose hemoglobin level falls below 10 g/dL have his/her REBETOL dose reduced to 600 mg daily (1 × 200-mg capsule AM, 2 × 200-mg capsules PM). A patient whose hemoglobin level falls below 8.5 g/dL should be permanently discontinued from REBETOL/INTRON A therapy. (See **WARNINGS**.)

It is recommended that a patient who experiences moderate depression (persistent low mood, loss of interest, poor self image, and/or hopelessness) have his/her INTRON A dose temporarily reduced and/or be considered for medical therapy. A patient experiencing severe depression or suicidal ideation/attempt should be discontinued from REBETOL/INTRON A therapy and followed closely with appropriate medical management. (See **WARNINGS**.)

[See table 9 above]

Administration of INTRON A Injection

At the discretion of the physician, the patient may self-administer the INTRON A. (See illustrated **MEDICATION GUIDE** for instructions.)

The INTRON A Injection is supplied as a clear and colorless solution. The appropriate INTRON A dose should be withdrawn from the vial or set on the multidose pen and injected subcutaneously. The INTRON A Injection supplied with the B-D Safety Lok™ syringes contain a plastic sleeve to be pulled over the needle after use. The syringe locks with an audible click when the green stripe on the safety sleeve covers the red stripe on the needle. After administration of INTRON A Injection, it is essential to follow the procedure for proper disposal of syringes and needles. (See **MEDICATION GUIDE** for detailed instructions.)

[See second table above]

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. INTRON A Injection may be administered using either sterilized glass or plastic disposable syringes.

Stability INTRON A Injection provided in vials is stable at 35°C (95°F) for up to 7 days and at 30°C (86°F) for up to 14 days. INTRON A Injection provided in a multidose pen is stable at 30°C (86°F) for up to 2 days. The solution is clear and colorless.

HOW SUPPLIED

REBETOL 200-mg Capsules are white, opaque capsules with REBETOL, 200 mg, and the Schering Corporation logo imprinted on the capsule shell; the capsules are packaged in a bottle.

INTRON A Injection is a clear, colorless solution packaged in single-dose and multidose vials, and a multidose pen.

INTRON A Injection and REBETOL Capsules are available in the following combination package presentations:

[See third table above]

STORAGE CONDITIONS

Store the REBETOL Capsules plus INTRON A Injection combination package refrigerated between 2° and 8°C (36° and 46°F).

When separated, the individual bottle of REBETOL Capsules should be stored refrigerated between 2° and 8°C (36° and 46°F) or at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

When separated, the individual vials of INTRON A Injection and the INTRON A multidose pen should be stored refrigerated between 2° and 8°C (36°and 46°F).

Schering Corporation
Kenilworth, NJ 07033 USA

B-25930622 Rev. 10/03
25272935T

RIBAVIRIN ℞

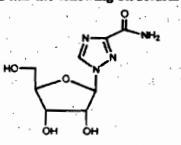
[ri-bə-vi-rin]

USP Capsules Caps

- **Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication. (See WARNINGS.)**
- **The primary toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. (See WARNINGS, ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION.)**
- **Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple-dose half-life of 12 days, and so it may persist in nonplasma compartments for as long as 6 months. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month posttreatment follow-up period. (See CONTRAINDICATIONS, WARNINGS, PRECAUTIONS–Information for Patients and Pregnancy Category X.)**

DESCRIPTION

Ribavirin is a nucleoside analog. The chemical name of ribavirin is 1-β- D-ribofuranosyl-1 *H*-1,2,4-triazole-3-carboxamide and has the following structural formula:



Continued on next page

Ribavirin is a white, crystalline powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. The empirical formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.21.

Ribavirin Capsules consist of a white powder in a white, opaque, gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of gelatin, sodium lauryl sulfate, silicon dioxide, and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink which is made of shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C Blue #2 aluminum lake.

Mechanism of Action

The mechanism of inhibition of hepatitis C virus (HCV) RNA by combination therapy with ribavirin and interferon products has not been established.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Ribavirin Single- and multiple-dose pharmacokinetic properties in adults are summarized in **TABLE 1**. Ribavirin was rapidly and extensively absorbed following oral administration. However, due to first-pass metabolism, the absolute bioavailability averaged 64% (44%). There was a linear relationship between dose and AUC_{tf}(AUC from time zero to last measurable concentration) following single doses of 200-1200 mg ribavirin. The relationship between dose and C_{max} was curvilinear, tending to asymptote above single doses of 400-600 mg.

Upon multiple oral dosing, based on $AUC12_{hr}$, a sixfold accumulation of ribavirin was observed in plasma. Following oral dosing with 600 mg BID, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 (37%) ng/mL. Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which probably reflects slow elimination from nonplasma compartments.

Effect of Food on Absorption of Ribavirin Both AUC_{tf} and C_{max} increased by 70% when Ribavirin Capsules were administered with a high-fat meal (841 kcal), 53.8 g fat, 31.6 g protein, and 57.4 g carbohydrate) in a single-dose pharmacokinetic study. There are insufficient data to address the clinical relevance of these results. Clinical efficacy studies with Ribavirin/INTRON® A (interferon alfa-2b) were conducted without instructions with respect to food consumption. During clinical studies with Ribavirin/PEG-INTRON® (peginterferon), all subjects were instructed to take Ribavirin Capsules with food. (See **DOSAGE AND ADMINISTRATION**.)

Effect of Antacid on Absorption of Ribavirin Coadministration of Ribavirin Capsules with an antacid containing magnesium, aluminum, and simethicone (Mylanta®[1]) resulted in a 14% decrease in mean ribavirin AUC_{tf}. The clinical relevance of results from this single-dose study is unknown.

TABLE 1. Mean (% CV) Pharmacokinetic Parameters for Ribavirin When Administered Individually to Adults

Parameter	Ribavirin (N = 12)	
	Single Dose 600 mg Capsules (N = 12)	Multiple Dose 600 mg BID Capsules (N = 12)
T_{max}(hr)	1.7 (46)***	3 (60)
C_{max}*	782 (37)	3680 (85)
AUC_{tf}**	13400 (48)	228000 (25)
T½ (hr)	43.6 (47)	298 (30)
Apparent Volume of Distribution (L)	2825 (9)†	
Apparent Clearance (L/hr)	38.2 (40)	
Absolute Bioavailability	64% (44)††	

* ng/mL
** ng.hr/mL
*** N = 11
† data obtained from a single-dose pharmacokinetic study using ^{14}C labeled ribavirin; N = 5
†† N = 6

Ribavirin transport into nonplasma compartments has been most extensively studied in red blood cells, and has been identified to be primarily via an e_s-type equilibrative nucleoside transporter. This type of transporter is present on virtually all cell types and may account for the extensive volume of distribution. Ribavirin does not bind to plasma proteins.

Ribavirin has two pathways of metabolism: (i) a reversible phosphorylation pathway in nucleated cells; and (ii) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally. After oral administration of 600 mg of ^{14}C-ribavirin, approximately 61% and 12% of the radioactivity was eliminated in the urine and feces, respectively, in 336 hours. Unchanged ribavirin accounted for 17% of the administered dose.

TABLE 3. Virologic and Histologic Responses: Previously Untreated Patients*

	US Study			
	24 weeks of treatment		48 weeks of treatment	
	INTRON A plus Ribavirin (N = 228)	INTRON A plus Placebo (N = 231)	INTRON A plus Ribavirin (N = 228)	INTRON A plus Placebo (N = 225)
Virologic Response				
-Responder[1]	65 (29)	13 (6)	85 (37)	27 (12)
-Nonresponder	147 (64)	194 (84)	110 (48)	168 (75)
-Missing Data	16 (7)	24 (10)	33 (14)	30 (13)
Histologic Response				
-Improvement[2]	102 (45)	77 (33)	96 (42)	65 (29)
-No improvement	77 (34)	99 (43)	61 (27)	93 (41)
-Missing Data	49 (21)	55 (24)	71 (31)	67 (30)
	International Study			
	24 weeks of treatment		48 weeks of treatment	
	INTRON A plus Ribavirin (N = 265)		INTRON A plus Ribavirin (N = 268)	INTRON A plus Placebo (N = 266)
Virologic Response				
-Responder[1]	86 (32)		113 (42)	46 (17)
-Nonresponder	158 (60)		120 (45)	196 (74)
-Missing Data	21 (8)		35 (13)	24 (9)
Histologic Response				
-Improvement[2]	103 (39)		102 (38)	69 (26)
-No improvement	85 (32)		58 (22)	111 (41)
-Missing Data	77 (29)		108 (40)	86 (32)

* Number (%) of patients.
1. Defined as HCV RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period.
2. Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of ≥2 points.

Results of *in vitro* studies using both human and rat liver microsome preparations indicated little or no cytochrome P450 enzyme-mediated metabolism of ribavirin, with minimal potential for P450 enzyme-based drug interactions.

No pharmacokinetic interactions were noted between INTRON A Injection and Ribavirin Capsules in a multiple-dose pharmacokinetic study.

Drug Interactions

Ribavirin has been shown *in vitro* to inhibit phosphorylation of zidovudine and stavudine which could lead to decreased antiretroviral activity. Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is coadminstered with ribavirin, which could cause or worsen clinical toxicities (see **PRECAUTIONS: Drug Interactions**).

1. Trademark of Johnson & Johnson-Merck Consumer Pharmaceuticals Co.

Special Populations

Renal Dysfunction The pharmacokinetics of ribavirin were assessed after administration of a single oral dose (400 mg) of ribavirin to non HCV-infected subjects with varying degrees of renal dysfunction. The mean AUC_{tf} value was threefold greater in subjects with creatinine clearance values between 10 to 30 mL/min when compared to control subjects (creatinine clearance >90 mL/min). In subjects with creatinine clearance values between 30 to 60 mL/min, AUC_{tf} was twofold greater when compared to control subjects. The increased AUC_{tf} appears to be due to reduction of renal and non-renal clearance in these patients. Phase III efficacy trials included subjects with creatinine clearance values >50 mL/min. The multiple dose pharmacokinetics of ribavirin cannot be accurately predicted in patients with renal dysfunction. Ribavirin is not effectively removed by hemodialysis. Patients with creatinine clearance <50 mL/min should not be treated with ribavirin (see **WARNINGS**.)

Hepatic Dysfunction The effect of hepatic dysfunction was assessed after a single oral dose of ribavirin (600 mg). The mean AUC_{tf} values were not significantly different in subjects with mild, moderate, or severe hepatic dysfunction (Child-Pugh Classification A, B, or C) when compared to control subjects. However, the mean C_{max} values increased with severity of hepatic dysfunction and was twofold greater in subjects with severe hepatic dysfunction when compared to control subjects.

Elderly Patients Pharmacokinetic evaluations in elderly subjects have not been performed.

Gender There were no clinically significant pharmacokinetic differences noted in a single-dose study of eighteen male and eighteen female subjects.

Pediatric Patients Multiple-dose pharmacokinetic properties for Ribavirin Capsules and INTRON A in pediatric patients with chronic hepatitis C between 5 and 16 years of age are summarized in **Table 2**. The pharmacokinetics of Ribavirin and INTRON A (dose-normalized) are similar in adults and pediatric patients. Ribavirin C_{min} values were similar following administration of Ribavirin Capsules during 48 weeks of therapy in pediatric patients (3 to 16 years of age).

TABLE 2. Mean (% CV) Multiple-Dose Pharmacokinetic Parameters for INTRON A and Ribavirin Capsules When Administered to Pediatric Patients with Chronic Hepatitis C

Parameter	Ribavirin 15 mg/kg/day as 2 divided doses (N = 17)	INTRON A 3 MIU/m² TIW (N = 54)
T_{max}(hr)	1.9 (83)	5.9 (36)
C_{max}(ng/mL)	3275 (25)	51 (48)
AUC*	29774 (26)	622 (48)
Apparent clearance L/hr/kg	0.27 (27)	ND

*AUC_{12}(ng.hr/mL) for Ribavirin; AUC_{0-24}(IU.hr/mL) for INTRON A
ND = not done

**** In this section of the label, numbers in parenthesis indicate % coefficient of variation.***

INDICATIONS AND USAGE

Adult Use

Ribavirin, USP Capsules are indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients 18 years of age and older with compensated liver disease previously untreated with alpha interferon and in patients 18 years of age and older who have relapsed following alpha interferon therapy.

Ribavirin Capsules are indicated in combination with PEG-INTRON (peginterferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age.

The safety and efficacy of Ribavirin Capsules with interferons other than INTRON A or PEG-INTRON products have not been established.

Pediatric Use

Ribavirin Capsules are indicated in combination with INTRON A (interferon alfa-2b, recombinant) Injection for the treatment of chronic hepatitis C in patients 5 years of age and older with compensated liver disease previously untreated with alpha interferon and in patients who have relapsed following alpha interferon therapy.

Evidence of disease progression, such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load, should be considered when

onses:

y

48 weeks of treatment	
INTRON A plus Ribavirin (N = 228)	INTRON A plus Placebo (N = 225)
85 (37)	27 (12)
110 (48)	168 (75)
33 (14)	30 (13)
96 (42)	65 (29)
61 (27)	93 (41)
71 (31)	67 (30)

Study

48 weeks of treatment	
INTRON A plus Ribavirin (N = 268)	INTRON A plus Placebo (N = 266)
113 (42)	46 (17)
120 (45)	196 (74)
35 (13)	24 (9)
102 (38)	69 (26)
58 (22)	111 (41)
108 (40)	86 (32)

PCR assay at end of treatment and during

y Knodell HAI score (I+II+III) improvement

iatric patients. Ribavirin C_{min} values were
g administration of Ribavirin Capsules dur-
therapy in pediatric patients (3 to 16 years

an (% CV) Multiple-Dose Pharmacokinetic
s for INTRON A and Ribavirin Capsules
Administered to Pediatric Patients
with Chronic Hepatitis C

	Ribavirin 15 mg/kg/day as 2 divided doses (N = 17)	INTRON A 3 MIU/m² TIW (N = 54)
	1.9 (83)	5.9 (36)
	3275 (25)	51 (48)
	29774 (26)	622 (48)
nce L/hr/kg	0.27 (27)	ND

L) for Ribavirin; AUC_{0-24}(IU.hr/mL) for

*of the label, numbers in parenthesis indi-
ent of variation.*

AND USAGE

Capsules are indicated in combination with
erferon alfa-2b, recombinant) Injection for
chronic hepatitis C in patients 18 years of
th compensated liver disease previously un-
ha interferon and in patients 18 years of
bo have relapsed following alpha interferon

ules are indicated in combination with
peginterferon alfa-2b, recombinant) Injec-
ment of chronic hepatitis C in patients with
er disease who have not been previously
erferon alpha and are at least 18 years of

fficacy of Ribavirin Capsules with interfer-
NTRON A or PEG-INTRON products have
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ules are indicated in combination with
erferon alfa-2b, recombinant) Injection for
chronic hepatitis C in patients 5 years of
ch compensated liver disease previously un-
ha interferon and in patients who have re-
alpha interferon therapy.
ase progression, such as hepatic inflamma-
as well as prognostic factors for response,
nd viral load, should be considered when

deciding to treat a pediatric patient. The benefits of treatment should be weighed against the safety findings observed (see **PRECAUTIONS Pediatric Use**) for pediatric subjects in the clinical trials.

Description of Clinical Studies

Ribavirin/INTRON A Combination Therapy

Adult Patients

Previously Untreated Patients

Adults with compensated chronic hepatitis C and detectable HCV RNA (assessed by a central laboratory using a research-based RT-PCR assay) who were previously untreated with alpha interferon therapy were enrolled into two multicenter, double-blind trials (US and International) and randomized to receive Ribavirin Capsules 1200 mg/day (1000 mg/day for patients weighing ≤75 kg) plus INTRON A Injection 3 MIU TIW or INTRON A Injection plus placebo for 24 or 48 weeks followed by 24 weeks of off-therapy follow-up. The International study did not contain a 24-week INTRON A plus placebo treatment arm. The US study enrolled 912 patients who, at baseline, were 67% male, 89% Caucasian with a mean Knodell HAI score (I+II+III) of 7.5, and 72% genotype 1. The International study, conducted in Europe, Israel, Canada, and Australia, enrolled 799 patients (65% male, 95% Caucasian, mean Knodell score 6.8, and 58% genotype 1).

Study results are summarized in **TABLE 3**.

[See table 3 at top of previous page]

Of patients who had not achieved HCV RNA below the limit of detection of the research based assay by week 24 of Ribavirin/INTRON A treatment, less than 5% responded to an additional 24 weeks of combination treatment.

Among patients with HCV Genotype 1 treated with Ribavirin/INTRON A therapy who achieved HCV RNA below the detection limit of the research-based assay by 24 weeks, those randomized to 48 weeks of treatment had higher virologic responses compared to those in the 24 week treatment group. There was no observed increase in response rates for patients with HCV nongenotype 1 randomized to Ribavirin/INTRON A therapy for 48 weeks compared to 24 weeks.

Relapse Patients

Patients with compensated chronic hepatitis C and detectable HCV RNA (assessed by a central laboratory using a research-based RT-PCR assay) who had relapsed following one or two courses of interferon therapy (defined as abnormal serum ALT levels) were enrolled into two multi-center, double-blind trials (US and International) and randomized to receive ribavirin 1200 mg/day (1000 mg/day for patients weighing ≤75 kg) plus INTRON A 3 MIU TIW or INTRON A plus placebo for 24 weeks followed by 24 weeks of off-therapy follow-up. The US study enrolled 153 patients who, at baseline, were 67% male, 92% Caucasian with a mean Knodell HAI score (I+II+III) of 6.8, and 58% genotype 1. The International study, conducted in Europe, Israel, Canada, and Australia, enrolled 192 patients (64% male, 95% Caucasian, mean Knodell score 6.6, and 56% genotype 1).

Study results are summarized in **TABLE 4**.

[See table 4 above]

Virologic and histologic responses were similar among male and female patients in both the previously untreated and relapse studies.

Pediatric Patients

Pediatric patients 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV RNA (assessed by a central laboratory using a research-based RT-PCR assay) were treated with Ribavirin 15 mg/kg per day plus INTRON A 3 MIU/m² TIW for 48 weeks followed by 24 weeks of off-therapy follow-up. A total of 118 patients received treatment who were 57% male, 80% Caucasian, and 78% genotype 1. Patients <5 years of age received Ribavirin Oral Solution and those >5 years of age received either Ribavirin Oral Solution or Capsules. Study results are summarized in **TABLE 5**.

TABLE 5. Virologic Response: Previously Untreated Pediatric Patients*

	INTRON A 3 MIU/m² TIW Plus Ribavirin 15 mg/kg/day
Overall Response[1] (n = 118)	54 (46)
Genotype 1 (n = 92)	33 (36)
Genotype non-1 (n = 26)	21 (81)

* Number (%) of patients.

[1] Defined as HCV RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.

Patients with viral genotype 1, regardless of viral load, had a lower response rate to INTRON A/Ribavirin combination therapy compared to patients with genotype non-1, 36% versus 81%. Patients with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 26% (13/50).

Ribavirin/PEG-INTRON Combination Therapy

A randomized study compared treatment with two PEG-INTRON/Ribavirin regimens [PEG-INTRON 1.5 µg/kg SC once weekly (QW)/Ribavirin 800 mg PO daily (in divided doses); PEG-INTRON 1.5 µg/kg SC QW for 4 weeks then 0.5 µg/kg SC QW for 44 weeks/Ribavirin 1000/1200 mg PO daily (in divided doses)] with INTRON A [3 MIU SC thrice weekly (TIW)/Ribavirin 1000/1200 mg PO daily (in divided doses)] in 1530 adults with chronic hepatitis C. Interferon naïve patients were treated for 48 weeks and followed for 24 weeks posttreatment. Eligible patients had compensated liver disease, detectable HCV RNA, elevated ALT, and liver histopathology consistent with chronic hepatitis.

Response to treatment was defined as undetectable HCV RNA at 24 weeks posttreatment (see **Table 6**).

TABLE 6. Rates of Response to Combination Treatment

	PEG-INTRON 1.5µg/kg QW Ribavirin 800 mg QD	INTRON A 3 MIU TIW Ribavirin 1000/1200 mg QD
Overall[1,2] response	52% (264/511)	46% (231/505)
Genotype 1	41% (141/348)	33% (112/343)
Genotype 2-6	75% (123/163)	73% (119/162)

[1] Serum HCV RNA was measured with a research-based quantitative polymerase chain reaction assay by a central laboratory.

[2] Difference in overall treatment response (PEG-INTRON/Ribavirin vs. INTRON A/Ribavirin) is 6% with 95% confidence interval of (0.18, 11.63) adjusted for viral genotype and presence of cirrhosis at baseline.

The response rate to PEG-INTRON 1.5→0.5µg/kg/Ribavirin was essentially the same as the response to INTRON A/Ribavirin (data not shown).

Patients with viral genotype 1, regardless of viral load, had a lower response rate to PEG-INTRON (1.5 µg/kg)/Ribavirin combination therapy compared to patients with other viral genotypes. Patients with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 30% (78/256) compared to a response rate of 29% (71/247) with INTRON A/Ribavirin combination therapy.

Patients with lower body weight tended to have higher adverse event rates (see **ADVERSE REACTIONS**) and higher response rates than patients with higher body weights. Differences in response rates between treatment arms did not substantially vary with body weight.

Treatment response rates with PEG-INTRON/Ribavirin combination therapy were 49% in men and 56% in women. Response rates were lower in African American and Hispanic patients and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of poor prognostic factors compared to Caucasians the number of non-Caucasians studied (11% of the total) was insufficient to allow meaningful conclusions about differences in response rates after adjusting for prognostic factors.

Liver biopsies were obtained before and after treatment in 68% of patients. Compared to baseline approximately 2/3 of patients in all treatment groups were observed to have a modest reduction in inflammation.

TABLE 4. Virologic and Histologic Responses: Relapse Patients*

	US Study		International Study	
	INTRON A plus Ribavirin (N = 77)	INTRON A plus Placebo (N = 76)	INTRON A plus Ribavirin (N = 96)	INTRON A plus Placebo (N = 96)
Virologic Response				
-Responder[1]	33 (43)	3 (4)	46 (48)	5 (5)
-Nonresponder	36 (47)	66 (87)	45 (47)	91 (95)
-Missing Data	8 (10)	7 (9)	5 (5)	0 (0)
Histologic Response				
-Improvement[2]	38 (49)	27 (36)	49 (51)	30 (31)
-No improvement	23 (30)	37 (49)	29 (30)	44 (46)
-Missing Data	16 (21)	12 (16)	18 (19)	22 (23)

* Number (%) of patients.

1. Defined as HCV RNA below limit of detection using a research based RT-PCR assay at end of treatment and during follow-up period.
2. Defined as posttreatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of ≥2 points.

CONTRAINDICATIONS

Pregnancy

Ribavirin Capsules may cause birth defects and/or death of the exposed fetus. Ribavirin therapy is contraindicated for use in women who are pregnant or in men whose female partners are pregnant. (See **WARNINGS, PRECAUTIONS—Information for Patients and Pregnancy Category X.**)

Ribavirin Capsules are contraindicated in patients with a history of hypersensitivity to ribavirin or any component of the capsule.

Patients with autoimmune hepatitis must not be treated with combination Ribavirin/INTRON A therapy because using these medicines can make the hepatitis worse.

Patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia) should not be treated with Ribavirin Capsules.

WARNINGS

Based on results of clinical trials ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection; therefore, Ribavirin Capsules must not be used alone. The safety and efficacy of Ribavirin Capsules have only been established when used together with INTRON A (interferon alfa-2b, recombinant) as REBETRON Combination Therapy or with PEG-INTRON Injection.

There are significant adverse events caused by Ribavirin/INTRON A or PEG-INTRON therapy, including severe depression and suicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, pulmonary dysfunction, pancreatitis, and diabetes. Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up. The REBETRON Combination Therapy and PEG-INTRON package inserts should be reviewed in their entirety prior to initiation of combination treatment for additional safety information.

Pregnancy

Ribavirin Capsules may cause birth defects and/or death of the exposed fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin has demonstrated significant teratogenic and/or embryocidal effects in all animal species in which adequate studies have been conducted. These effects occurred at doses as low as one twentieth of the recommended human dose of ribavirin. RIBAVIRIN THERAPY SHOULD NOT BE STARTED UNTIL A REPORT OF A NEGATIVE PREGNANCY TEST HAS BEEN OBTAINED IMMEDIATELY PRIOR TO PLANNED INITIATION OF THERAPY. Patients should be instructed to use at least two forms of effective contraception during treatment and during the six month period after treatment has been stopped based on multiple dose half-life of ribavirin of 12 days. Pregnancy testing should occur monthly during ribavirin therapy and for six months after therapy has stopped (see CONTRAINDICATIONS and PRECAUTIONS: Information for Patients and Pregnancy Category X).

Anemia

The primary toxicity of ribavirin is hemolytic anemia, which was observed in approximately 10% of Ribavirin /INTRON A-treated patients in clinical trials (see ADVERSE REACTIONS: Laboratory Values– Hemoglobin). The anemia associated with Ribavirin Capsules occurs within 1-2 weeks of initiation of therapy. BECAUSE THE INITIAL DROP IN HEMOGLOBIN MAY BE SIGNIFICANT, IT IS ADVISED THAT HEMOGLOBIN OR HEMATOCRIT BE OBTAINED PRETREATMENT AND AT WEEK 2 AND WEEK 4 OF THERAPY, OR MORE FREQUENTLY IF CLINICALLY INDICATED. Patients should then be followed as clinically appropriate.

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with preexisting cardiac disease should have electrocardiograms administered before treatment, and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued. (See DOSAGE AND ADMINISTRATION: Guidelines for Dose Modification.) Because cardiac disease may be worsened by drug induced anemia, patients with a history of significant or unstable cardiac disease should not use ribavirin. (See ADVERSE REACTIONS.)

Continued on next page

Ribavirin and INTRON A or PEG-INTRON therapy should be suspended in patients with signs and symptoms of pancreatitis and discontinued in patients with confirmed pancreatitis.

Ribavirin should not be used in patients with creatinine clearance <50 mL/min. (See **Clinical Pharmacology, Special Populations**.)

Pulmonary

Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis and pneumonia, have been reported during therapy with Ribavirin/INTRON A; occasional cases of fatal pneumonia have occurred. In addition, sarcoidosis or the exacerbation of sarcoidosis has been reported. If there is evidence of pulmonary infiltrates or pulmonary function impairment, the patient should be closely monitored, and if appropriate, combination Ribavirin/INTRON A treatment should be discontinued.

PRECAUTIONS

The safety and efficacy of Ribavirin/INTRON A and PEG-INTRON therapy for the treatment of HIV infection, adenovirus, RSV, parainfluenza, or influenza infections have not been established. Ribavirin Capsules should not be used for these indications. Ribavirin for inhalation has a separate package insert, which should be consulted if ribavirin inhalation therapy is being considered.

The safety and efficacy of Ribavirin/INTRON A therapy has not been established in liver or other organ transplant patients, patients with decompensated liver disease due to hepatitis C infection, patients who are non-responders to interferon therapy, or patients coinfected with HBV or HIV.

Information for Patients

Patients must be informed that Ribavirin Capsules may cause birth defects and/or death of the exposed fetus. Ribavirin must not be used by women who are pregnant or by men whose female partners are pregnant. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking ribavirin. Ribavirin should not be initiated until a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Patients must perform a pregnancy test monthly during therapy and for 6 months posttherapy. Women of childbearing potential must be counseled about use of effective contraception (two reliable forms) prior to initiating therapy. Patients (male and female) must be advised of the teratogenic/embryocidal risks and must be instructed to practice effective contraception during ribavirin and for 6 months posttherapy. Patients (male and female) should be advised to notify the physician immediately in the event of a pregnancy. (See **CONTRAINDICATIONS** and **WARNINGS**.)

If pregnancy does occur during treatment or during 6 months post-therapy, the patient must be advised of the teratogenic risk of ribavirin therapy to the fetus. Patients, or partners of patients, should immediately report any pregnancy that occurs during treatment or within 6 months after treatment cessation to their physician. Physicians should report such cases by calling 1-800-593-2214.

Patients receiving Ribavirin Capsules should be informed of the benefits and risks associated with treatment, directed in its appropriate use, and referred to the patient **MEDICATION GUIDE**. Patients should be informed that the effect of treatment of hepatitis C infection on transmission is not known, and that appropriate precautions to prevent transmission of the hepatitis C virus should be taken.

The most common adverse experience occurring with Ribavirin Capsules is anemia, which may be severe. (See **ADVERSE REACTIONS**.) Patients should be advised that laboratory evaluations are required prior to starting therapy and periodically thereafter. (See **Laboratory Tests**.) It is advised that patients be well hydrated, especially during the initial stages of treatment.

Laboratory Tests The following laboratory tests are recommended for all patients treated with Ribavirin Capsules, prior to beginning treatment and then periodically thereafter.

- Standard hematologic tests - including hemoglobin (pretreatment, week 2 and week 4 of therapy, and as clinically appropriate [see **WARNINGS**]), complete and differential white blood cell counts, and platelet count.
- Blood chemistries - liver function tests and TSH.
- Pregnancy - including monthly monitoring for women of childbearing potential.
- ECG (see **WARNINGS**)

Carcinogenesis and Mutagenesis Ribavirin did not cause an increase in any tumor type when administered for 6 months in the transgenic p53 deficient mouse model at doses up to 300 mg/kg (estimated human equivalent of 25 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 1.9 times the maximum recommended human daily dose). Ribavirin was non-carcinogenic when administered for 2 years to rats at doses up to 40 mg/kg (estimated human equivalent of 5.71 mg/kg based on body surface area adjustment for a 60 kg adult). However, this dose was less than the maximum tolerated dose, and therefore the study was not adequate to fully characterize the carcinogenic potential of ribavirin.

Ribavirin demonstrated increased incidences of mutation and cell transformation in multiple genotoxicity assays. Ribavirin was active in the Balb/3T3 *In Vitro* Cell Transformation Assay. Mutagenic activity was observed in the mouse lymphoma assay, and at doses of 20-200 mg/kg (estimated human equivalent of 1.67-16.7 mg/kg, based on body surface area adjustment for a 60 kg adult; 0.1-1 × the maximum recommended human 24-hour dose of ribavirin) in a mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes.

Impairment of Fertility Ribavirin demonstrated significant embryocidal and/or teratogenic effects at doses well below the recommended human dose in all animal species in which adequate studies have been conducted.

Fertile women and partners of fertile women should not receive ribavirin unless the patient and his/her partner are using effective contraception (two reliable forms). Based on a multiple dose half-life ($t_{1/2}$) of ribavirin of 12 days, effective contraception must be utilized for 6 months posttherapy (eg, 15 half-lives of clearance for ribavirin).

Ribavirin should be used with caution in fertile men. In studies in mice to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 15 to 150 mg/kg/day (estimated human equivalent of 1.25-12.5 mg/kg/day, based on body surface area adjustment for a 60 kg adult; 0.1-0.8 × the maximum human 24-hour dose of ribavirin) administered for 3 or 6 months, abnormalities in sperm occurred. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity was apparent within 1 or 2 spermatogenesis cycles.

Animal Toxicology Long-term studies in the mouse and rat (18-24 months; doses of 20-75 and 10-40 mg/kg/day, respectively (estimated human equivalent doses of 1.67-6.25 and 1.43-5.71 mg/kg/day, respectively, based on body surface area adjustment for a 60 kg adult; approximately 0.1-0.4 × the maximum human 24-hour dose of ribavirin)) have demonstrated a relationship between chronic ribavirin exposure and increased incidences of vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in controls, but the incidence was increased in ribavirin-treated rats.

Pregnancy Category X (see CONTRAINDICATIONS)

Ribavirin produced significant embryocidal and/or teratogenic effects in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced. In conventional embryotoxicity/teratogenicity studies in rats and rabbits, observed no effect dose levels were well below those for proposed clinical use (0.3 mg/kg/day for both the rat and rabbit; approximately 0.06 × the recommended human 24-hour dose of ribavirin). No maternal toxicity or effects on offspring were observed in a peri/postnatal toxicity study in rats dosed orally at up to 1 mg/kg/day (estimated human equivalent dose of 0.17 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 0.01 × the maximum recommended human 24-hour dose of ribavirin).

Treatment and Posttreatment: Potential Risk to the Fetus Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. It is not known whether ribavirin contained in sperm will exert a potential teratogenic effect upon fertilization of the ova. In a study in rats, it was concluded that dominant lethality was not induced by ribavirin at doses up to 200 mg/kg for 5 days (estimated human equivalent doses of 7.14-28.6 mg/kg, based on body surface area adjustment for a 60 kg adult; up to 1.7 × the maximum recommended human dose of ribavirin). However, because of the potential human teratogenic effects of ribavirin, male patients should be advised to take every precaution to avoid risk of pregnancy for their female partners.

TABLE 7. Selected Treatment-Emergent Adverse Events: Previously Untreated and Relapse Adult Patients and Previously Untreated Pediatric Patients

	Percentage of Patients						
	US Previously Untreated Study				US Relapse Study		Pediatric Patients
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment		48 weeks of treatment
Patients Reporting Adverse Events*	INTRON A plus Ribavirin (N = 228)	INTRON A plus Placebo (N = 231)	INTRON A plus Ribavirin (N = 228)	INTRON A plus Placebo (N = 225)	INTRON A plus Ribavirin (N = 77)	INTRON A plus Placebo (N = 76)	INTRON A plus Ribavirin (N = 118)
Application Site Disorders							
Injection Site Inflammation	13	10	12	14	6	8	14
Injection Site Reaction	7	9	8	9	5	3	19
Body as a Whole – General Disorders							
Headache	63	63	66	67	66	68	69
Fatigue	68	62	70	72	60	53	58
Rigors	40	32	42	39	43	37	25
Fever	37	35	41	40	32	36	61
Influenza-Like Symptoms	14	18	18	20	13	13	31
Asthenia	9	4	9	9	10	4	5
Chest Pain	5	4	9	8	6	7	5
Central & Peripheral Nervous System Disorders							
Dizziness	17	15	23	19	26	21	20
Gastrointestinal System Disorders							
Nausea	38	35	46	33	47	33	33
Anorexia	27	16	25	19	21	14	51
Dyspepsia	14	6	16	9	16	9	<1
Vomiting	11	10	9	13	12	8	42
Musculoskeletal System Disorders							
Myalgia	61	57	64	63	61	58	32
Arthralgia	30	27	33	36	29	29	15
Musculoskeletal Pain	20	26	28	32	22	28	21
Psychiatric Disorders							
Insomnia	39	27	39	30	26	25	14
Irritability	23	19	32	27	25	20	10
Depression	32	25	36	37	23	14	13
Emotional Lability	7	6	11	8	12	8	16
Concentration Impaired	11	14	14	14	10	12	5
Nervousness	4	2	4	4	5	4	3
Respiratory System Disorders							
Dyspnea	19	9	18	10	17	12	5
Sinusitis	9	7	10	14	12	7	<1
Skin and Appendages Disorders							
Alopecia	28	27	32	28	27	26	23
Rash	20	9	28	8	21	5	17
Pruritus	21	9	19	8	13	4	12
Special Senses, Other Disorders							
Taste Perversion	7	4	8	4	6	5	<1

*Patients reporting one or more adverse events. A patient may have reported more than one adverse event within a body system/organ class category.

events.
ıtre ıted Pediatric Patients

Patients

	US Relapse Study		Pediatric Patients
	24 weeks of treatment		48 weeks of treatment
A	INTRON A plus Ribavirin (N = 77)	INTRON A plus Placebo (N = 76)	INTRON A plus Ribavirin (N = 118)
)			
	6	8	14
	5	3	19
	66	68	69
	60	53	58
	43	37	25
	32	36	61
	13	13	31
	10	4	5
	6	7	5
	26	21	20
	47	33	33
	21	14	51
	16	9	<1
	12	8	42
	61	58	32
	29	29	15
	22	28	21
	26	25	14
	25	20	10
	23	14	13
	12	8	16
	10	12	5
	5	4	3
	17	12	5
	12	7	<1
	27	26	23
	21	5	17
	13	4	12
	6	5	<1

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ıs) in mice. In rats, retinal degeneration
ıls, but the incidence was increased in
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animal species in which adequate studies
ted. Malformations of the skull, palate,
skeleton, and gastrointestinal tract were
ıce and severity of teratogenic effects in-
ıtion of the drug dose. Survival of fetuses
reduced. In conventional embryotoxicity/
ies in rats and rabbits, observed no effect
ell below those for proposed clinical use
both the rat and rabbit; approximately
ıended human 24-hour dose of ribavirin).
ty or effects on offspring were observed in
ıxicity study in rats dosed orally at up to
timated human equivalent dose of
on body surface area adjustment for a
oximately 0.01 × the maximum recom-
-hour dose of ribavirin).

Posttreatment: Potential Risk to the

ıs known to accumulate in intracellular
where it is cleared very slowly. It is not
ıvirin contained in sperm will exert a po-
effect upon fertilization of the ova. In a
ıs concluded that dominant lethality was
ıvirin at doses up to 200 mg/kg for 5 days
ı equivalent doses of 7.14-28.6 mg/kg.
ace area adjustment for a 60 kg adult; up
ıum recommended human dose of ribavi-
ause of the potential human teratogenic
, male patients should be advised to take
ı avoid risk of pregnancy for their female

Women of childbearing potential should not receive ribavirin unless they are using effective contraception (two reliable forms) during the therapy period. In addition, effective contraception should be utilized for 6 months post-therapy based on a multiple-dose half-life ($t_{1/2}$) of ribavirin of 12 days.

Male patients and their female partners must practice effective contraception (two reliable forms) during treatment with ribavirin and for the 6-month posttherapy period (eg, 15 half-lives for ribavirin clearance from the body).

Ribavirin Pregnancy Registry

Ribavirin Pregnancy Registry: A Ribavirin Pregnancy Registry has been established to monitor maternal-fetal outcomes of pregnancies in female patients and female partners of male patients exposed to ribavirin during treatment and for six months following cessation of treatment. Physicians and patients are encouraged to report such cases by calling 1-800-593-2214.

Nursing Mothers It is not known whether the ribavirin product is excreted in human milk. Because of the potential for serious adverse reactions from the drug in nursing infants, a decision should be made whether to discontinue nursing or to delay or discontinue ribavirin.

Geriatric Use Clinical studies of Ribavirin/INTRON A or PEG-INTRON therapy did not include sufficient numbers of subjects aged 65 and over to determine if they respond differently from younger subjects.

Ribavirin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients often have decreased renal function, care should be taken in dose selection. Renal function should be monitored and dosage adjustments should be made accordingly. Ribavirin should not be used in patients with creatinine clearance <50 mL/min. (See **WARNINGS**.)

In general, Ribavirin Capsules should be administered to elderly patients cautiously, starting at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic and/or cardiac function, and of concomitant disease or other drug therapy. In clinical trials, elderly subjects had a higher frequency of anemia (67%) than did younger patients (28%). (See **WARNINGS**.)

Pediatric Use

Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up (see WARNINGS). As in adult patients, pediatric patients experienced other psychiatric adverse events (eg, depression, emotional lability, somnolence); anemia, and neutropenia (see **WARNINGS**). During a 48-week course of therapy there was a decrease in the rate of linear growth (mean percentile assignment decrease of 9%) and a decrease in the rate of weight gain (mean percentile assignment decrease of 13%). A general reversal of these trends was noted during the 24-week posttreatment period.

Drug Interactions

Didanosine: Coadministration of Ribavirin Capsules and didanosine is not recommended. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactactemia/lactic acidosis have been reported in clinical trials (see **CLINICAL PHARMACOLOGY: Drug Interactions**).

Stavudine and Zidovudine: Ribavirin may antagonize the *in vitro* antiviral activity of stavudine and zidovudine against HIV. Therefore, concomitant use of ribavirin with either of these drugs should be used with caution (see **CLINICAL PHARMACOLOGY: Drug Interactions**).

ADVERSE REACTIONS

The primary toxicity of ribavirin is hemolytic anemia. Reductions in hemoglobin levels occurred within the first 1-2 weeks of oral therapy. (See WARNINGS.) Cardiac and pulmonary events associated with anemia occurred in approximately 10% of patients. (See **WARNINGS**.)

Ribavirin/INTRON A Combination Therapy

In clinical trials, 19% and 6% of previously untreated and relapse patients, respectively, discontinued therapy due to adverse events in the combination arms compared to 13% and 3% in the interferon arms. Selected treatment-emergent adverse events that occurred in the US studies with ≥5% incidence are provided in **Table 7** by treatment group. In general, the selected treatment-emergent adverse events were reported with lower incidence in the international studies as compared to the US studies with the exception of asthenia, influenza-like symptoms, nervousness, and pruritus.

Pediatric Patients

In clinical trials of 118 pediatric patients 3 to 16 years of age, 6% discontinued therapy due to adverse events. Dose modifications were required in 30% of patients, most commonly for anemia and neutropenia. In general, the adverse event profile in the pediatric population was similar to that observed in adults. Injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in pediatric patients compared to adult patients. Conversely, pediatric patients experienced less fatigue, dyspepsia, arthralgia, insomnia, irritability, impaired concentration, dyspnea, and pruritus compared to adult patients. Selected treatment-emergent adverse events that occurred with ≥5% incidence among all pediatric patients who received the recommended dose of Ribavirin/INTRON A combination therapy are provided in **Table 7**.

[See table 7 at top of previous page]

TABLE 9. Selected Hematologic Values During Treatment with Ribavirin plus INTRON A: Previously Untreated and Relapse Adult Patients and Previously Untreated Pediatric Patients[17]

	Percentage of Patients						
	US Previously Untreated Study				US Relapse Study		Pediatric Patients
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment		48 weeks of treatment
	INTRON A plus Ribavirin (N = 228)	INTRON A plus Placebo (N = 231)	INTRON A plus Ribavirin (N = 228)	INTRON A plus Placebo (N = 225)	INTRON A plus Ribavirin (N = 77)	INTRON A plus Placebo (N = 76)	INTRON A plus Ribavirin (N = 118)
Hemoglobin (g/dL)							
9.5-10.9	24	1	32	1	21	3	24
8.0-9.4	5	0	4	0	4	0	3
6.5-7.9	0	0	0	0.4	0	0	0
<6.5	0	0	0	0	0	0	0
Leukocytes ($\times 10^9$/L)							
2.0-2.9	40	20	38	23	45	26	35
1.5-1.9	4	1	9	2	5	3	8
1.0-1.4	0.9	0	2	0	0	0	0
<1.0	0	0	0	0	0	0	0
Neutrophils ($\times 10^9$/L)							
1.0-1.49	30	32	31	44	42	34	37
0.75-0.99	14	15	14	11	16	18	15
0.5-0.74	9	9	14	7	8	4	16
<0.5	11	8	11	5	5	8	3
Platelets ($\times 10^9$/L)							
70-99	9	11	11	14	6	12	0.8
50-69	2	3	2	3	0	5	2
30-49	0	0.4	0	0.4	0	0	0
<30	0.9	0	1	0.9	0	0	0
Total Bilirubin (mg/dL)							
1.5-3.0	27	13	32	13	21	7	2
3.1-6.0	0.9	0.4	2	0	3	0	0
6.1-12.0	0	0	0.4	0	0	0	0
>12.0	0	0	0	0	0	0	0

In addition, the following spontaneous adverse events have been reported during the marketing surveillance of Ribavirin/INTRON A therapy: hearing disorder and vertigo.

Ribavirin/PEG-INTRON Combination Therapy

Overall, in clinical trials, 14% of patients receiving Ribavirin in combination with PEG-INTRON, discontinued therapy compared with 13% treated with Ribavirin in combination with INTRON A. The most common reasons for discontinuation of therapy were related to psychiatric, systemic (eg, fatigue, headache), or gastrointestinal adverse events. Adverse events that occurred in clinical trial at >5% incidence are provided in **Table 8** by treatment group. Safety and effectiveness of Ribavirin in combination with PEG-INTRON has not been established in pediatric patients.

TABLE 8. Adverse Events Occurring in > 5% of Patients

	*Percentage of Patients Reporting Adverse Events**	
Adverse Events	**PEG-INTRON 1.5 µg/kg/ Ribavirin (N = 511)**	**INTRON A/ Ribavirin (N = 505)**
Application Site		
Injection Site Inflammation	25	18
Injection Site Reaction	58	36
Autonomic Nervous System		
Mouth Dry	12	8
Sweating Increased	11	7
Flushing	4	3
Body as a Whole		
Fatigue/Asthenia	66	63
Headache	62	58
Rigors	48	41
Fever	46	33
Weight Decrease	29	20
RUQ Pain	12	6
Chest Pain	8	7
Malaise	4	6
Central/Peripheral Nervous System		
Dizziness	21	17
Endocrine		
Hypothyroidism	5	4
Gastrointestinal		
Nausea	43	33
Anorexia	32	27
Diarrhea	22	17
Vomiting	14	12
Abdominal Pain	13	13
Dyspepsia	9	8
Constipation	5	5
Hematologic Disorders		
Neutropenia	26	14
Anemia	12	17
Leukopenia	6	5
Thrombocytopenia	5	2
Liver and Biliary System		
Hepatomegaly	4	4
Musculoskeletal		
Myalgia	56	50
Arthralgia	34	28
Musculoskeletal Pain	21	19
Psychiatric		
Insomnia	40	41
Depression	31	34
Anxiety/Emotional Lability/Irritability	47	47
Concentration Impaired	17	21
Agitation	8	5
Nervousness	6	6
Reproductive, Female		
Menstrual Disorder	7	6
Resistance Mechanism		
Infection Viral	12	12
Infection Fungal	6	1
Respiratory System		
Dyspnea	26	24
Coughing	23	16
Pharyngitis	12	13
Rhinitis	8	6
Sinusitis	6	5
Skin and Appendages		
Alopecia	36	32
Pruritus	29	28
Rash	24	23
Skin Dry	24	23

Continued on next page

Information on Schering products appearing on these pages is effective as of August 2007.

Ribavirin—Cont.

Special Senses, Other		
Taste Perversion	9	4
Vision Disorders		
Vision Blurred	5	6
Conjunctivitis	4	5

*Patients reporting one or more adverse events. A patient may have reported more than one adverse event within a body system/organ class category.

Laboratory Values

Ribavirin/INTRON A Combination Therapy

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below. (See **TABLE 9.**)

Hemoglobin Hemoglobin decreases among patients receiving ribavirin therapy began at Week 1, with stabilization by Week 4. In previously untreated patients treated for 48 weeks the mean maximum decrease from baseline was 3.1 g/dL in the US study and 2.9 g/dL in the International study. In relapse patients the mean maximum decrease from baseline was 2.8 g/dL in the US study and 2.6 g/dL in the International study. Hemoglobin values returned to pretreatment levels within 4-8 weeks of cessation of therapy in most patients.

Bilirubin and Uric Acid Increases in both bilirubin and uric acid, associated with hemolysis, were noted in clinical trials. Most were moderate biochemical changes and were reversed within 4 weeks after treatment discontinuation. This observation occurs most frequently in patients with a previous diagnosis of Gilbert's syndrome. This has not been associated with hepatic dysfunction or clinical morbidity.

[See table 9 at top of previous page]

Ribavirin/PEG-INTRON Combination Therapy

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below. (See **TABLE 10.**)

Hemoglobin

Ribavirin induced a decrease in hemoglobin levels in approximately two thirds of patients. Hemoglobin levels decreased to <11g/dL in about 30% of patients. Severe anemia (<8 g/dL) occurred in <1% of patients. Dose modification was required in 9 and 13% of patients in the PEG-INTRON/Ribavirin and INTRON A/Ribavirin groups.

Bilirubin and Uric Acid

In the Ribavirin/PEG-INTRON combination trial 10-14% of patients developed hyperbilirubinemia and 33-38% developed hyperuricemia in association with hemolysis. Six patients developed mild to moderate gout.

TABLE 10. Selected Hematologic Values During Treatment with Ribavirin plus PEG-INTRON

	Number (%) of Subjects	
	PEG-INTRON plus Ribavirin (N = 511)	**INTRON A plus Ribavirin (N = 505)**
Hemoglobin (g/dL)		
9.5–10.9	26	27
8.0–9.4	3	3
6.5–7.9	0.2	0.2
<6.5	0	0
Leukocytes ($\times 10^9$/L)		
2.0–2.9	46	41
1.5–1.9	24	8
1.0–1.4	5	1
<1.0	0	0
Neutrophils ($\times 10^9$/L)		
1.0–1.49	33	37
0.75–0.99	25	13
0.5–0.74	18	7
<0.5	4	2
Platelets ($\times 10^9$/L)		
70–99	15	5
50–69	3	0.8
30–49	0.2	0.2
<30	0	0
Total Bilirubin (mg/dL)		
1.5–3.0	10	13
3.1–6.0	0.6	0.2
6.1–12.0	0	0.2
>12.0	0	0
ALT (SGPT)		
2 × Baseline	0.6	0.2
2.1–5 × Baseline	3	1
5.1–10 × Baseline	0	0
>10 × Baseline	0	0

OVERDOSAGE

There is limited experience with overdosage. Acute ingestion of up to 20 grams of Ribavirin Capsules, INTRON A ingestion of up to 120 million units, and subcutaneous doses of INTRON A up to 10 times the recommended doses have been reported. Primary effects that have been observed are increased incidence and severity of the adverse events related to the therapeutic use of INTRON A and Ribavirin. However, hepatic enzyme abnormalities, renal failure, hemorrhage, and myocardial infarction have been reported with administration of single subcutaneous doses of INTRON A that exceed dosing recommendations.

There is no specific antidote for INTRON A or Ribavirin, and hemodialysis and peritoneal dialysis are not effective for treatment of overdose of either agent.

DOSAGE AND ADMINISTRATION

(see **CLINICAL PHARMACOLOGY, Special Populations**; see WARNINGS).

Ribavirin/INTRON A Combination Therapy

Adults

The recommended dose of Ribavirin Capsules depends on the patient's body weight. The recommended dose of ribavirin is provided in **TABLE 11.**

The recommended duration of treatment for patients previously untreated with interferon is 24 to 48 weeks. The duration of treatment should be individualized to the patient depending on baseline disease characteristics, response to therapy, and tolerability of the regimen. (See **Description of Clinical Studies** and **ADVERSE REACTIONS**.) After 24 weeks of treatment virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV RNA below the limit of detection of the assay by 24 weeks. There are no safety and efficacy data on treatment for longer than 48 weeks in the previously untreated patient population.

In patients who relapse following non-pegylated interferon monotherapy, the recommended duration of treatment is 24 weeks. There are no safety and efficacy data on treatment for longer than 24 weeks in the relapse patient population.

TABLE 11. Recommended Dosing

Body weight	Ribavirin Capsules
≤ 75 kg	2 × 200-mg capsules AM, 3 × 200-mg capsules PM daily p.o.
> 75 kg	3 × 200-mg capsules AM, 3 × 200-mg capsules PM daily p.o.

Pediatrics

The recommended dose of ribavirin is 15 mg/kg per day orally (divided dose AM and PM). For children weighing ≤25 kg or who cannot swallow capsules, Ribavirin Oral Solution is supplied in a concentration of 40 mg/mL. For children weighing >25 kg, either the Oral Solution or 200-mg capsule may be administered. Refer to **Table 12** for dosing recommendations for the 200-mg capsule to achieve the recommended dose.

The recommended duration of treatment is 48 weeks for pediatric patients with genotype 1. After 24 weeks of treatment, virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV RNA below the limit of detection of the assay by this time. The recommended duration of treatment for pediatric patients with genotype 2/3 is 24 weeks. There are no safety and efficacy data on treatment for longer than 48 weeks in pediatrics.

[See table 12 below]

TABLE 12. Pediatric Dosing

Body weight	Ribavirin Capsules	INTRON A Injection
25-36 kg	1 × 200-mg capsules AM, 1 × 200-mg capsules PM daily p.o.	3 million IU/m^2 3 times weekly s.c.
37-49 kg	1 × 200-mg capsules AM, 2 × 200-mg capsules PM daily p.o.	3 million IU/m^2 3 times weekly s.c.
50-61 kg	2 × 200-mg capsules AM, 2 × 200-mg capsules PM daily p.o.	3 million IU/m^2 3 times weekly s.c.
>61 kg	Refer to adult dosing table	Refer to adult dosing table

Ribavirin may be administered without regard to food, but should be administered in a consistent manner with respect to food intake. (See **CLINICAL PHARMACOLOGY**.)

Ribavirin/PEG-INTRON Combination Therapy

The recommended dose of Ribavirin Capsules is 800 mg/day in 2 divided doses: two capsules (400 mg) in the morning with food and two capsules (400 mg) in the evening with food.

Dose Modifications (TABLE 13)

If severe adverse reactions or laboratory abnormalities develop during combination Ribavirin/INTRON A therapy the dose should be modified, or discontinued if appropriate, until the adverse reactions abate. If intolerance persists after dose adjustment, Ribavirin/INTRON A therapy should be discontinued.

Ribavirin should not be used in patients with creatinine clearance <50 mL/min. (See **WARNINGS** and **CLINICAL PHARMACOLOGY, Special Populations**.)

Ribavirin should be administered with caution to patients with pre-existing cardiac disease. Patients should be assessed before commencement of therapy and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be stopped. (See **WARNINGS**.)

For patients with a history of stable cardiovascular disease a permanent dose reduction is required if the hemoglobin decreases by ≥2 g/dL during any 4-week period. In addition for these cardiac history patients, if the hemoglobin remains <12 g/dL after 4 weeks on a reduced dose, the patient should discontinue combination Ribavirin/INTRON A therapy.

It is recommended that a patient whose hemoglobin level falls below 10 g/dL have his/her ribavirin dose reduced to 600 mg daily (1 × 200-mg capsule AM, 2 × 200-mg capsules PM) for adults and 7.5 mg/kg per day (divided dose AM and PM) for pediatric patients. A patient whose hemoglobin level falls below 8.5 g/dL should be permanently discontinued from ribavirin therapy. (See **WARNINGS**.)

TABLE 13. Guidelines for Dose Modifications and Discontinuation for Anemia

Hemoglobin	Dose Reduction* Ribavirin-600 mg daily adults 7.5 mg/kg daily for pediatrics	Permanent Discontinuation of Ribavirin Treatment
No Cardiac History	**<10 g/dL**	**<8.5 g/dL**
Cardiac History Patients	**≥2 g/dL decrease during any 4-week period during treatment**	**<12 g/dL after 4 weeks of dose reduction**

HOW SUPPLIED

Ribavirin 200-mg Capsules are white, opaque capsules with 200 mg and W-1523 imprinted on the capsule shell; the capsules are packaged in a bottle containing 42 capsules (NDC-5 9930-1523-4), 56 capsules (NDC 59930-1523-3), 70 capsules (NDC 59930-1523-2), and 84 capsules (NDC 59930-1523-1).

Storage Conditions

The bottle of Ribavirin Capsules should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

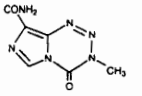
Warrick Pharmaceuticals Corporation
Reno, NV 89506 USA

26964245 Rev. 3/04

TEMODAR®
[tĕm-ō-dăr]
(temozolomide)
CAPSULES

DESCRIPTION

TEMODAR Capsules for oral administration contain temozolomide, an imidazotetrazine derivative. The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-as-tetrazine-8-carboxamide. The structural formula is:



The material is a white to light tan/light pink powder with a molecular formula of $C_6H_6N_8O_2$ and a molecular weight of 194.15. The molecule is stable at acidic pH (<5), and labile at pH >7, hence TEMODAR can be administered orally. The prodrug, temozolomide, is rapidly hydrolyzed to the active 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH.

Each capsule contains either 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg of temozolomide. The inactive ingredients for TEMODAR Capsules are lactose anhydrous, colloi-

Attachment C

Roche

®PEGASYS®
(peginterferon alfa-2a)

℞ only

Alpha interferons, including PEGASYS (peginterferon alfa-2a), may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping PEGASYS therapy (see WARNINGS and ADVERSE REACTIONS).

Use with Ribavirin. Ribavirin, including COPEGUS®, may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen (see COPEGUS Package Insert for additional information and other WARNINGS).

DESCRIPTION

PEGASYS, peginterferon alfa-2a, is a covalent conjugate of recombinant alfa-2a interferon (approximate molecular weight [MW] 20,000 daltons) with a single branched bis-monomethoxy polyethylene glycol (PEG) chain (approximate MW 40,000 daltons). The PEG moiety is linked at a single site to the interferon alfa moiety via a stable amide bond to lysine. Peginterferon alfa-2a has an approximate molecular weight of 60,000 daltons. Interferon alfa-2a is produced using recombinant DNA technology in which a cloned human leukocyte interferon gene is inserted into and expressed in *Escherichia coli*.

PEGASYS is supplied as an injectable solution in vials and prefilled syringes.

180 µg/1.0 mL Vial: A vial contains approximately 1.2 mL of solution to deliver 1.0 mL of drug product. Subcutaneous (sc) administration of 1.0 mL delivers 180 µg of drug product (expressed as the amount of interferon alfa-2a), 8.0 mg sodium chloride, 0.05 mg polysorbate 80, 10.0 mg benzyl alcohol, 2.62 mg sodium acetate trihydrate, and 0.05 mg acetic acid. The solution is colorless to light yellow and the pH is 6.0 ± 0.5.

180 µg/0.5 mL Prefilled Syringe: Each syringe contains 0.6 mL of solution to deliver 0.5 mL of drug product. Subcutaneous (sc) administration of 0.5 mL delivers 180 µg of drug product (expressed as the amount of interferon alfa-2a), 4.0 mg sodium chloride, 0.025 mg polysorbate 80, 5.0 mg benzyl alcohol, 1.3085 mg sodium acetate trihydrate, and 0.0231 mg acetic acid. The solution is colorless to light yellow and the pH is 6.0 ± 0.5.

ADVERSE REACTIONS

PEGASYS alone or in combination with COPEGUS causes a broad variety of serious adverse reactions (see **BOXED WARNING** and **WARNINGS**). The most common life-threatening or fatal events induced or aggravated by PEGASYS and COPEGUS were depression, suicide, relapse of drug abuse/overdose, and bacterial infections, each occurring at a frequency of <1%. Hepatic decompensation occurred in 2% (10/574) of CHC/HIV patients (see **WARNINGS: Hepatic Failure and Hepatitis Exacerbations**).

In all hepatitis C studies, one or more serious adverse reactions occurred in 10% of CHC monoinfected patients and in 19% of CHC/HIV patients receiving PEGASYS alone or in combination with COPEGUS. The most common serious adverse event (3% in CHC and 5% in CHC/HIV) was bacterial infection (e.g., sepsis, osteomyelitis, endocarditis, pyelonephritis, pneumonia). Other SAEs occurred at a frequency of <1% and included: suicide, suicidal ideation, psychosis, aggression, anxiety, drug abuse and drug overdose, angina, hepatic dysfunction, fatty liver, cholangitis, arrhythmia, diabetes mellitus, autoimmune phenomena (e.g., hyperthyroidism, hypothyroidism, sarcoidosis, systemic lupus erythematosus, rheumatoid arthritis), peripheral neuropathy, aplastic anemia, peptic ulcer, gastrointestinal bleeding, pancreatitis, colitis, corneal ulcer, pulmonary embolism, coma, myositis, cerebral hemorrhage, thrombotic thrombocytopenic purpura, psychotic disorder, and hallucination.

Nearly all patients in clinical trials experienced one or more adverse events. For hepatitis C patients, the most commonly reported adverse reactions were psychiatric reactions, including depression, insomnia, irritability, anxiety, and flu-like symptoms such as fatigue, pyrexia, myalgia, headache, and rigors. Other common reactions were anorexia, nausea and vomiting, diarrhea, arthralgias, injection site reactions, alopecia, and pruritus.

Overall 11% of CHC monoinfected patients receiving 48 weeks of therapy with PEGASYS either alone or in combination with COPEGUS discontinued therapy; 16% of CHC/HIV coinfected patients discontinued therapy. The most common reasons for discontinuation of therapy were psychiatric, flu-like syndrome (e.g., lethargy, fatigue, headache), dermatologic, and gastrointestinal disorders and laboratory abnormalities (thrombocytopenia, neutropenia, and anemia).

Overall 39% of patients with CHC or CHC/HIV required modification of PEGASYS and/or COPEGUS therapy. The most common reason for dose modification of PEGASYS in CHC and CHC/HIV patients was for laboratory abnormalities, neutropenia (20% and 27%, respectively) and thrombocytopenia (4% and 6%, respectively). The most common reason for dose modification of COPEGUS in CHC and CHC/HIV patients was anemia (22% and 16%, respectively).

PEGASYS dose was reduced in 12% of patients receiving 1000 mg to 1200 mg COPEGUS for 48 weeks and in 7% of patients receiving 800 mg COPEGUS for 24 weeks. COPEGUS dose was reduced in 21% of patients receiving 1000 mg to 1200 mg COPEGUS for 48 weeks and in 12% of patients receiving 800 mg COPEGUS for 24 weeks.

Chronic hepatitis C monoinfected patients treated for 24 weeks with PEGASYS and 800 mg COPEGUS were observed to have lower incidence of serious adverse events (3% vs. 10%), Hgb <10 g/dL (3% vs. 15%), dose modification of PEGASYS (30% vs. 36%) and COPEGUS (19% vs. 38%) and of withdrawal from treatment (5% vs. 15%) compared to patients treated for 48 weeks with PEGASYS and 1000 mg or 1200 mg COPEGUS. On the other hand the overall incidence of adverse events appeared to be similar in the two treatment groups.

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug. Also, the adverse event rates listed here may not predict the rates observed in a broader patient population in clinical practice.

MEDICATION GUIDE
PEGASYS®
(peginterferon alfa-2a)

Before you start taking PEGASYS (PEG-ah-sis), alone or in combination with COPEGUS® (Co-PEG-UHS), please read this Medication Guide carefully. Read this Medication Guide each time you refill your prescription in case new information has been added and make sure the pharmacist has given you the medicine your healthcare provider prescribed for you. Reading the information in this Medication Guide does not take the place of talking with your healthcare provider.

If you are taking PEGASYS in combination with COPEGUS, you should also read the Medication Guide for COPEGUS (ribavirin, USP) Tablets.

What is the most important information I should know about PEGASYS therapy?
PEGASYS, taken alone or in combination with COPEGUS, is a treatment for some people who are infected with hepatitis C virus. PEGASYS taken alone is a treatment for some people who are infected with the hepatitis B virus. However, PEGASYS and COPEGUS can have serious side effects that may cause death in rare cases. Before starting PEGASYS therapy, you should talk with your healthcare provider about the possible benefits and the possible side effects of treatment, to decide if either of these treatments is right for you. If you begin treatment you will need to see your healthcare provider regularly for examinations and blood tests to make sure your treatment is working and to check for side effects.

The most serious possible side effects of PEGASYS taken alone or in combination with COPEGUS include:

Risks to Pregnancy:
Taking PEGASYS in combination with COPEGUS tablets can cause death, serious birth defects or other harm to your unborn child. Therefore, if you are pregnant or your partner is pregnant or plans to become pregnant, do not take PEGASYS/COPEGUS combination therapy. Female patients and female partners of male patients being treated with PEGASYS/COPEGUS combination therapy must not become pregnant during treatment and for 6 months after treatment has stopped. During this time, you must have pregnancy tests that show you are not pregnant. You must also use two effective forms of birth control during therapy and for 6 months after stopping therapy. Male patients should use a condom with spermicide as one of the two forms. You must use birth control even if you believe that you are not fertile or that your fertility is low. You should talk to your healthcare provider about birth control for you and your partner.

If you are pregnant, you or your male partner must not take PEGASYS/COPEGUS combination therapy. If you or your partner are being treated and you become pregnant either during treatment or within 6 months of stopping treatment, call your healthcare provider right away.

If you or a female sexual partner becomes pregnant, you should tell your healthcare provider. There is a Ribavirin Pregnancy Registry that collects information about pregnancy outcomes of female patients and female partners of male patients exposed to ribavirin. You or your healthcare provider are encouraged to contact the Registry at 1-800-593-2214.

Mental health problems:
PEGASYS may cause some patients to develop mood or behavioral problems. Signs of these problems include irritability (getting easily upset), depression (feeling low, feeling bad about yourself or feeling hopeless), and anxiety. Some patients may have aggressive behavior. Some patients may develop thoughts about ending their lives (suicidal thoughts) and may attempt to do so. A few patients have even ended their lives. Former drug addicts may fall back into drug addiction or overdose. You must tell your healthcare provider if you are being treated for a mental illness or have a history of mental illness or if you are or have ever been addicted to drugs or alcohol. Call your healthcare provider immediately if you develop any of these problems while on PEGASYS treatment.

Blood problems:
Many patients taking PEGASYS have had a drop in the number of their white blood cells and their platelets. If the numbers of these blood cells are too low, you could be at risk for serious infections or bleeding.

COPEGUS causes a decrease in the number of your red blood cells (anemia). This can be dangerous, especially for patients who already have heart or circulatory (cardiovascular) problems. If you have or have ever had any cardiovascular problems, talk with your healthcare provider before taking the combination of PEGASYS and COPEGUS.

Liver problems:
Infrequently, some patients with hepatitis C and liver scarring can develop sudden severe worsening (failure) of their liver disease while taking PEGASYS. Patients infected with both the hepatitis C virus and HIV can have an increased chance of having liver failure during PEGASYS treatment.

Some patients taking PEGASYS for hepatitis B have had a rise in a blood test that measures liver inflammation. If you have a rise in this blood test, your liver may need to be watched more closely with additional blood tests.

WARNINGS

General

Patients should be monitored for the following serious conditions, some of which may become life threatening. Patients with persistently severe or worsening signs or symptoms should have their therapy withdrawn (see **BOXED WARNING**).

Neuropsychiatric

Life-threatening or fatal neuropsychiatric reactions may manifest in patients receiving therapy with PEGASYS and include suicide, suicidal ideation, homicidal ideation, depression, relapse of drug addiction, and drug overdose. These reactions may occur in patients with and without previous psychiatric illness.

PEGASYS should be used with extreme caution in patients who report a history of depression. Neuropsychiatric adverse events observed with alpha interferon treatment include aggressive behavior, psychoses, hallucinations, bipolar disorders, and mania. Physicians should monitor all patients for evidence of depression and other psychiatric symptoms. Patients should be advised to report any sign or symptom of depression or suicidal ideation to their prescribing physicians. In severe cases, therapy should be stopped immediately and psychiatric intervention instituted (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Infections

While fever may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of high or persistent fever must be ruled out, particularly in patients with neutropenia. Serious and severe infections (bacterial, viral, fungal), some fatal, have been reported during treatment with alpha interferons including Pegasys. Appropriate anti-infective therapy should be started immediately and discontinuation of therapy should be considered.

Bone Marrow Toxicity

PEGASYS suppresses bone marrow function and may result in severe cytopenias. Ribavirin may potentiate the neutropenia and lymphopenia induced by alpha interferons including PEGASYS. Very rarely alpha interferons may be associated with aplastic anemia. It is advised that complete blood counts (CBC) be obtained pre-treatment and monitored routinely during therapy (see **PRECAUTIONS: Laboratory Tests**).

PEGASYS and COPEGUS should be used with caution in patients with baseline neutrophil counts <1500 cells/mm^3, with baseline platelet counts <90,000 cells/mm^3 or baseline hemoglobin <10 g/dL. PEGASYS therapy should be discontinued, at least temporarily, in patients who develop severe decreases in neutrophil and/or platelet counts (see **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Severe neutropenia and thrombocytopenia occur with a greater incidence in HIV co-infected patients than monoinfected patients and may result in serious infections or bleeding (see **ADVERSE REACTIONS**).

Cardiovascular Disorders

Hypertension, supraventricular arrhythmias, chest pain, and myocardial infarction have been observed in patients treated with PEGASYS.

PEGASYS should be administered with caution to patients with pre-existing cardiac disease. Because cardiac disease may be worsened by ribavirin-induced anemia, patients with a history of significant or unstable cardiac disease should not use COPEGUS (see **WARNINGS: Anemia** and **COPEGUS Package Insert**).

Hepatic Failure and Hepatitis Exacerbations

Chronic hepatitis C (CHC) patients with cirrhosis may be at risk of hepatic decompensation and death when treated with alpha interferons, including PEGASYS. Cirrhotic CHC patients coinfected with HIV receiving highly active antiretroviral therapy (HAART) and interferon alfa-2a with or without ribavirin appear to be at increased risk for the development of hepatic decompensation compared to patients not receiving HAART. In Study 6, among 129 CHC/HIV cirrhotic patients receiving HAART, 14 (11%) of these patients across all treatment arms developed hepatic decompensation resulting in 6 deaths. All 14 patients were on NRTIs, including stavudine, didanosine, abacavir, zidovudine, and lamivudine. These small numbers of patients do not permit discrimination between specific NRTIs for the associated risk. During treatment, patients' clinical status and hepatic function should be closely monitored, and PEGASYS treatment should be immediately discontinued if decompensation (Child-Pugh score ≥6) is observed (see **CONTRAINDICATIONS**).

Exacerbations of hepatitis during hepatitis B therapy are not uncommon and are characterized by transient and potentially severe increases in serum ALT. Chronic hepatitis B patients experienced transient acute exacerbations (flares) of hepatitis B (ALT elevation >10-fold higher than the upper limit of normal) during PEGASYS treatment (12% and 18%) and post-treatment (7% and 12%) in HBeAg negative and HBeAg positive patients, respectively. Marked transaminase flares while on PEGASYS therapy have been accompanied by other liver test abnormalities. Patients experiencing ALT flares should receive more frequent monitoring of liver function. PEGASYS dose reduction should be considered in patients experiencing transaminase flares. If ALT increases are progressive despite reduction of PEGASYS dose or are accompanied by increased bilirubin or evidence of hepatic decompensation, PEGASYS should be immediately discontinued (see **ADVERSE REACTIONS: Chronic Hepatitis B** and **DOSAGE AND ADMINISTRATION: Dose Modifications**).

Hypersensitivity

Severe acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, and anaphylaxis) have been rarely observed during alpha interferon and ribavirin therapy. If such reaction occurs, therapy with PEGASYS and COPEGUS should be discontinued and appropriate medical therapy immediately instituted. Serious skin reactions including vesiculobullous eruptions, reactions in the spectrum of Stevens Johnson Syndrome (erythema multiforme major) with varying degrees of skin and mucosal involvement and exfoliative dermatitis (erythroderma) have been rarely reported in patients receiving PEGASYS with and without ribavirin. Patients developing signs or symptoms of severe skin reactions must discontinue therapy. (see **ADVERSE REACTIONS: Postmarketing Experience**).

Attachment D

MayoClinic.com
Tools for healthier lives

Original Article:http://www.mayoclinic.com/health/liver-cancer/DS00399

Liver cancer

Definition

Primary liver cancer begins in the cells of the liver itself. Although many cancers are declining in the United States, new cases of primary liver cancer are increasing.

In the United States, cancer affecting the liver is more commonly metastatic cancer, which occurs when tumors from other parts of the body spread (metastasize) to the liver. Cancers that commonly spread to the liver include colon, lung and breast cancers. These cancers aren't called liver cancer. Instead, they are named after the organ in which the cancer began — such as metastatic colon cancer to describe cancer that begins in the colon and spreads to the liver. These metastatic cancers are treated based on where the cancer began, rather than being treated as primary liver cancers.

Primary liver cancer is rarely discovered early and often doesn't respond to current treatments — thus, the prognosis is often poor. Even when treatments fail to provide much improvement in the liver cancer itself, pain and other signs and symptoms caused by liver cancer can be aggressively treated to improve quality of life. But the most important news about primary liver cancer is that you can greatly reduce your risk by protecting yourself from hepatitis infection and cirrhosis, the leading causes of the disease.

Symptoms

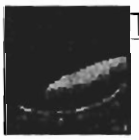
Most people don't have signs and symptoms in the early stages of liver cancer, which means the disease may not be detected until it's quite advanced. When symptoms do appear, they may include some or all of

the following:

- Loss of appetite and weight
- Abdominal pain, especially in the upper right part of your abdomen, that may extend into your back and shoulder
- Nausea and vomiting
- General weakness and fatigue
- An enlarged liver
- Abdominal swelling (ascites)
- A yellow discoloration of your skin and the whites of your eyes (jaundice)

Causes

CLICK TO ENLARGE


The liver

Your liver is a football-sized organ that sits in the upper right portion of your abdomen, beneath your diaphragm and above your stomach. Your liver processes most of the nutrients absorbed from your small intestine and determines how much sugar (glucose), protein and fat enter your bloodstream. It also manufactures blood-clotting substances and certain proteins. Your liver performs a vital detoxifying function by removing drugs, alcohol and other harmful substances from your bloodstream.

Liver cancer occurs when liver cells begin to grow abnormally. It's not completely understood why this happens, but researchers believe that cancer starts with damage to DNA — the material that contains the instructions for every chemical process in your body, including the rate of cellular growth. DNA damage causes changes in these instructions. One result is that cells may begin to grow out of control and eventually form a tumor — a mass of malignant cells.

Primary liver cancer
Primary liver cancer is divided into several types based on the type of cells that become cancerous. Types include:

- **Hepatocellular carcinoma (HCC).** This is the most common form of primary liver cancer in both children and adults. It starts in the hepatocytes, the main type of liver cell.
- **Cholangiocarcinoma.** This type of cancer begins in the small tube-like bile ducts within the liver. This type of cancer is sometimes called bile duct cancer.

- **Hepatoblastoma.** This rare type of liver cancer affects children younger than 4 years of age. Most children with hepatoblastoma can be successfully treated.
- **Angiosarcoma or hemangiosarcoma.** These rare cancers begin in the blood vessels of the liver and grow very quickly.

Metastatic cancer
In the United States, most cancer found in the liver has spread there from another part of the body. Rather than being referred to as liver cancer, this type of cancer is usually named after the organ where it originated and is described as "metastatic." For instance, cancer that has spread to the liver from the colon is referred to as metastatic colon cancer.

Metastatic cancers form when malignant cells detach from the primary cancer and travel through the body in the circulatory or lymphatic system. Cancers that begin in certain organs near the liver, such as the pancreas, can spread directly to the liver. Most metastatic cancers reach the liver through the bloodstream. Why the liver is so commonly affected by metastatic cancer isn't clear. One reason may be the liver's rich blood supply.

Risk factors

Primary liver cancer can affect people of all ages and races, but certain factors may increase your risk, including:

- **Sex.** Men are more likely to develop liver cancer than are women, though it isn't clear why.
- **Age.** In the United States and Europe, liver cancer diagnosis occurs on average at about age 60. People in Asia and Africa tend to be diagnosed with liver cancer at younger ages — between 20 and 50.
- **Chronic infection with HBV or HCV.** Chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is by far the most important risk factor for liver cancer.
- **Cirrhosis.** This progressive and irreversible condition causes scar tissue to form in your liver and increases your chances of developing liver cancer.
- **Diabetes.** People with this blood sugar disorder have a greater risk of liver cancer than do people who don't have diabetes. Having both diabetes and hepatitis C infection increases the risk even more.
- **Exposure to aflatoxins.** Consuming foods contaminated with fungi that produce aflatoxins greatly increases the risk of liver cancer. Crops such as corn, soybeans and peanuts can become contaminated with aflatoxins.

- **Excessive alcohol consumption.** Consuming more than a moderate amount of alcohol can lead to irreversible liver damage and increase your risk of liver cancer. Moderate consumption is defined as no more than two drinks a day for men and one drink for women. A drink is one 4- to 5-ounce glass of wine, 12 ounces of beer or a 1.5-ounce shot of 80-proof distilled spirits.
- **Smoking.** Smoking tobacco of any kind makes it more likely that you'll develop liver cancer.
- **Bile duct disease.** A disease called primary sclerosing cholangitis can cause inflammation and scarring of the liver's bile ducts. This increases your risk of bile duct cancer.

Tests and diagnosis

Screening

Screening for liver cancer hasn't been definitively proved to reduce the risk of dying of liver cancer. For this reason, many medical groups don't recommend liver cancer screening. However, the American Association for the Study of Liver Diseases recommends liver cancer screening for those thought to have a high risk, including people who have:

- Hepatitis B and one or more of the following: Are an Asian male older than 40, Asian female older than 50 or African and older than 20, have liver cirrhosis, or have a family history of liver cancer
- Liver cirrhosis from alcohol use
- Hepatitis C
- An inherited form of hemochromatosis
- Primary sclerosing cholangitis

Discuss the pros and cons of screening with your doctor. Together you can decide whether screening is right for you based on your risk. Screening typically involves blood tests and an ultrasound exam once or twice each year.

Diagnosis

If you experience any of the symptoms of liver cancer, your doctor will ask you about your medical history and perform a physical exam. Tests and procedures used to diagnose liver cancer include:

- **Ultrasound (ultrasonography).** This test uses sound waves to produce a picture of internal organs, including the liver. Ultrasound is painless and usually takes less than 30 minutes. While you lie on a bed or examining table, a wand-shaped device (transducer) is placed on your body. It emits sound waves that are reflected from

your liver and transformed into a computer image. Ultrasound provides information about the shape, texture and makeup of tumors.

- **Computerized tomography (CT) scan.** This test uses X-rays to produce cross-sectional images of your body. You may also have a variation of the test — known as a CT angiogram — in which contrast dye is injected into an artery in your liver. X-rays then track the dye as it flows through the blood vessels in your liver. A CT angiogram, which may take up to an hour to perform, can provide detailed information on the number and location of liver tumors, but a CT scan exposes you to more radiation than conventional X-rays do, and some people may experience an allergic reaction to the contrast dye.
- **Magnetic resonance imaging (MRI).** MRI creates images using a magnetic field and radio waves. Sometimes a contrast dye also may be used. The test can take from 15 minutes to an hour. Newer MRIs can show images of the ducts that transport bile from the liver to the upper part of the small intestine (duodenum) as well as of the arteries and veins within the liver.
- **Liver biopsy.** In this procedure, a sample of tissue is removed from your liver and examined under a microscope. Liver biopsy is considered the only definitive way to diagnose liver cancer. Your doctor may use a thin needle or a lighted instrument (laparoscope) to obtain the sample. Biopsy carries a risk of bleeding, bruising and infection.
- **Blood tests.** Doctors sometimes use a blood test that checks for the presence of alpha-fetoprotein (AFP) — a type of protein found in small amounts in adults — to detect liver cancer. But the test isn't perfect. Not all malignant liver tumors produce AFP, and those that do may be advanced by the time protein levels become elevated. In addition, other types of cancer and even some noncancerous liver diseases can raise AFP levels.

Staging

Staging tests help determine the size and location of cancer and whether it has spread. Liver cancer may be staged in different ways. One method uses the Roman numerals I through IV, with higher numbers indicating cancers that are more advanced. A stage I tumor is small and confined to one lobe of the liver. By stage IV, several tumors may exist in different lobes, or malignant cells may have spread to other parts of the body.

Doctors may also use the following stages to describe primary liver cancer in adults:

- **Localized resectable.** At this stage, the tumor is confined to one lobe of your liver and can be completely removed in an operation.

The term "resectable" refers to a tumor that can be surgically removed.

- **Localized unresectable.** The cancer is found in only one part of your liver, but can't be completely removed, either because the noncancerous portion of your liver isn't healthy or because the cancer is located near your liver's main arteries, veins and bile ducts.
- **Advanced.** This stage of cancer has spread throughout the liver or to other parts of your body, particularly the bones or lungs. You're more likely to have advanced cancer if you also have cirrhosis or chronic hepatitis.
- **Recurrent.** This means the cancer has returned to your liver or to another part of your body after being treated.

Stages of primary cancer in children
Doctors use the following stages to describe childhood liver cancer:

- **Stage I.** At this stage, the cancer can be removed with surgery.
- **Stage II.** Most stage II liver cancers can be removed with an operation, but microscopic amounts of cancer remain in the liver after surgery.
- **Stage III.** At this stage, some of the cancer may be surgically removed, but some will remain in the lymph nodes or abdomen.
- **Stage IV.** This stage of cancer has spread to other parts of the body.
- **Recurrent.** This means the cancer has returned after it has been treated. It may recur in the liver or in another part of the body.

Complications

People with liver cancer may sometimes experience the following complications:

- **Liver failure.** This occurs when the liver is no longer able to function adequately. It usually develops when there is extensive damage to liver cells.
- **Kidney failure.** The kidneys also may fail, losing their ability to filter fluids and waste and causing dangerous levels of these substances to accumulate in the body.
- **Spread of the cancer cells (metastasis).** Cancer that spreads to areas outside the liver becomes more difficult to treat. Liver cancer most commonly spreads to the lungs and bones.

Treatments and drugs

Treatments for primary liver cancer depend on the extent (stage) of the disease as well as your age, overall health, feelings and personal preferences. Discuss all of your options carefully with your treatment team.

The goal of any treatment is to eliminate the cancer completely. When that isn't possible, the focus may be on preventing the tumor from growing or spreading. In some cases palliative care only is appropriate. Palliative care refers to treatment aimed not at removing or slowing the disease but at helping relieve symptoms and making you as comfortable as possible.

Treatments for primary liver cancer in adults
Treatments for adults with primary liver cancer include:

- **Surgery.** The best treatment for localized resectable cancer is usually an operation known as surgical resection. In some cases, the area of the liver where the cancer is found can be completely removed. You aren't a candidate for surgical removal of liver tumors if you have cirrhosis or only a small amount of healthy liver tissue. Even when resections are successful, there is a chance the cancer can recur elsewhere in the liver or in other areas within a few years.
- **Alcohol injection.** In this procedure, pure alcohol is injected directly into tumors, either through the skin or during an operation. Alcohol dries out the cells of the tumor and eventually the cells die. Each treatment consists of one injection, although you may need a series of injections for the best results. Alcohol injection has been shown to improve survival in people with small hepatocellular tumors. It may also be used to help reduce symptoms in cases of metastatic liver cancer. The most common side effect is leaking of alcohol onto the liver or into the abdominal cavity.
- **Radiofrequency ablation.** In this procedure, electric current in the radiofrequency range is used to destroy malignant cells. Using an ultrasound or CT scan as a guide, your surgeon inserts several thin needles into small incisions in your abdomen. When the needles reach the tumor, they're heated with an electric current, destroying the malignant cells. Radiofrequency ablation is an option for people with small, unresectable hepatocellular tumors and for some types of metastatic liver cancers. Although the procedure has a somewhat higher risk of serious complications than alcohol injection does, it appears to provide better outcomes.
- **Chemoembolization.** Chemoembolization is a type of chemotherapy treatment that supplies strong anti-cancer drugs directly to the liver. Chemoembolization isn't curative, but it can shrink tumors in a certain percentage of people, which may provide

symptom relief and improve survival. During the procedure, the hepatic artery — the artery from which liver cancers derive their blood supply — is blocked, and chemotherapy drugs are injected between the blockage and the liver. The idea is that by targeting the tumor directly, doctors can use potent doses of drugs without creating as many side effects as occur with systemic chemotherapy. But the fact is that chemoembolization causes many of the same side effects as other forms of chemotherapy, including abdominal pain, nausea and vomiting. Chemoembolization is less likely to cause some side effects such as lowered blood cell counts or hair loss.

- **Cryoablation (cryosurgery or cryotherapy).** This treatment uses extreme cold to destroy cancer cells. Cryoablation may be an option for people with inoperable primary and metastatic liver cancers. It may also be used in addition to surgery, chemotherapy or other standard treatments. During the procedure, your doctor places an instrument (cryoprobe) containing liquid nitrogen directly onto liver tumors. Ultrasound images are used to guide the cryoprobe and monitor the freezing of the cells. Side effects include damage to the bile ducts and major blood vessels, leading to bleeding or infection.
- **Radiation therapy.** This treatment uses high-powered energy beams to destroy cancer cells and shrink tumors. Radiation may come from a machine outside your body or from radiation-containing materials inserted into your liver. Radiation may be used on its own to treat localized unresectable cancer. Or you may have radiation therapy following surgical removal of a tumor to help destroy any remaining malignant cells. Radiation side effects may include fatigue, nausea and vomiting.
- **Chemotherapy.** This treatment uses powerful drugs to kill cancer cells. Chemotherapy may be systemic — meaning it travels throughout your body in your bloodstream — or regional. Systemic chemotherapy is generally not effective in treating liver cancer, but may be a treatment option in certain cases.
- **Liver transplantation.** In this surgical procedure, a diseased liver is removed and replaced with a healthy, donated organ. Liver transplantation may be an option for some people with small, early-stage liver tumors and for certain people with bile duct tumors. In other cases, especially when tumors are larger or blood vessels are involved, a transplant may not improve long-term outlook because the cancer may recur outside the new liver.
- **Sorafenib (Nexavar).** Sorafenib was approved by the Food and Drug Administration in 2007 for use in advanced inoperable liver cancer. Sorafenib is a targeted therapy designed to interfere with a tumor's ability to generate new blood vessels. Sorafenib has been shown to slow or stop advanced liver cancer from progressing for a

few months longer than with no treatment. More studies are needed to understand how targeted therapies may be used to control advanced liver cancer.

Treatments for primary liver cancer in children
Liver cancer in young people is rare. As a result, most children with the disease are treated at centers that specialize in childhood cancers. In general, the treatments available for children are the same as for adults, and the best approach depends on the stage and type of cancer as well as the child's age and overall health.

Clinical trials
Because standard treatments often aren't effective in treating liver cancer, you may want to consider participating in a clinical trial — a research study that tries to improve current treatments or find new treatments. This can give you access to experimental therapies that might not otherwise be available. There are no guarantees with clinical trials, however, and you should fully understand the potential risks as well as possible benefits before taking this step.

Prevention

In many cases it's not possible to prevent the spread of cancer from another site to the liver. And it may not always be possible to prevent primary liver cancer. But you can greatly reduce your risk by taking steps to protect yourself from hepatitis B and C, cirrhosis and other liver diseases.

Get vaccinated
The single most effective way to prevent hepatitis B is to receive the hepatitis B vaccine, which provides more than 90 percent protection for both adults and children. Protection lasts years and may even be lifelong. The vaccine can be given to almost anyone, including infants, older adults and those with compromised immune systems. Infants often receive the vaccine in the first year of life — typically at 2, 4 and 9 months of age.

Take measures to prevent hepatitis C
Because no vaccine for hepatitis C exists, the following measures can play a key role in protecting your health:

- **Educate yourself and others.** Make sure you understand what viral hepatitis is and how it's transmitted.
- **Know the health status of any sexual partner.** Don't engage in unprotected sex unless you're absolutely certain your partner isn't infected with HBV, HCV or any other sexually transmitted disease. If you don't know the health status of your partner, use a new latex condom every time you have vaginal or anal sex. If you don't have a male condom, use a female condom.

- **Don't use IV drugs, but if you do, use a clean needle.** The best way to protect yourself from HCV is not to inject drugs. But if that isn't an option for you, make sure any needle you use is sterile, and don't share it. Contaminated drug paraphernalia is responsible for about half of all new hepatitis C cases. Take advantage of needle exchange programs in your community and consider seeking help for your drug use.
- **Avoid body piercing and tattooing.** Needles that may not be properly sterilized can spread the virus.
- **Be cautious about blood products in certain countries.** Most Americans with HCV became infected through blood transfusions received before 1992 — the year improved blood-screening tests became available. Although the blood supply is now well screened in the United States, this isn't always the case in other countries. If an emergency requires that you receive blood or blood products in another country, get tested for HCV and HBV as soon as you return home.
- **Avoid or limit alcohol.** Alcohol speeds the progression of any liver disease you may have and is the leading cause of cirrhosis — a key factor in primary liver cancer.
- **Avoid medications that may cause liver damage.** Your doctor can advise you about these medications, which may include over-the-counter medications as well as prescription drugs. Avoid mixing alcohol and acetaminophen (Tylenol, others) — a combination known to cause liver damage.
- **Avoid exposure to environmental toxins.** Your liver filters every substance you ingest, inhale or apply to your skin. For that reason, avoid unnecessary chemical exposure.

Coping and support

Learning you have any life-threatening illness can be devastating. But coping with a diagnosis of liver cancer can be especially difficult. The more advanced the disease when it's discovered, the less likely the chance of cure. As a result, you may feel overwhelmed just when you need to make crucial decisions. You're also likely to be even more concerned about others than yourself. How will you tell your children? Will your partner be able to cope? Who will take care of all of the things you normally do if you can't?

Although there are no easy answers for people dealing with liver cancer, some of the following suggestions may be of help:

- **Learn all you can about your illness.** Learn everything you can about liver cancer — how the disease progresses, your prognosis

and your treatment options, including both experimental and standard treatments and their side effects. Be sure you understand whether a particular approach is used to treat cancer or provide palliative care. Don't be afraid to seek a second opinion and to explore treatments available through clinical trials. You will have many decisions to make in the weeks and months ahead. The more you know, the more active role you can take in the decision-making process.

In addition to talking to your medical team, look for information in books and reputable sources on the Internet. The National Cancer Institute offers a toll-free information line called the Cancer Information Service. It provides access to trained counselors and accurate, up-to-date information on all aspects of living with cancer. You can reach the Cancer Information Service 24 hours a day at 800-4-CANCER, or 800-422-6237.

- **Maintain a strong support system.** Strong relationships are crucial in dealing with life-threatening illnesses. Although friends and family can be your best allies, in some cases they may have trouble dealing with your illness. Or you may not have a large social network. If so, the concern and understanding of a counselor, medical social worker or even a formal support group can be helpful. Although support groups aren't for everyone, they can sometimes be a good resource for practical information about your disease. You may also find strength and encouragement in being with people who are facing the same challenges you are.

  If you're interested in learning more about support groups, talk to a doctor, nurse, social worker or psychologist. They may be able to put you in touch with a group in your area. Or check your local phone book, library or a cancer organization. The National Cancer Institute also can provide a list of support groups. After deciding to participate in a group, try it out a few times. If it doesn't seem useful or comfortable, you don't have to continue.

- **Come to terms with your illness.** Coming to terms with your illness may be the hardest thing you've ever done. For some people, having a strong faith or a sense of something greater than themselves makes this process easier. Others seek counseling from someone who understands life-threatening illnesses, such as a medical social worker, psychologist or chaplain. Many people also take steps to ensure that their end-of-life wishes are known and respected.

By Mayo Clinic Staff

Jan. 9, 2008

DS00399

Attachment E

MayoClinic.com
Tools for healthier lives

Original Article:http://www.mayoclinic.com/health/hypothyroidism/DS00353

Hypothyroidism (underactive thyroid)

Definition

Hypothyroidism (underactive thyroid) is a condition in which your thyroid gland doesn't produce enough of certain important hormones.

Women, especially those older than 50, are more likely to have hypothyroidism. Hypothyroidism upsets the normal balance of chemical reactions in your body. It seldom causes symptoms in the early stages, but over time, untreated hypothyroidism can cause a number of health problems, such as obesity, joint pain, infertility and heart disease.

The good news is that accurate thyroid function tests are available to diagnose hypothyroidism, and treatment of hypothyroidism with synthetic thyroid hormone is usually simple, safe and effective once the proper dosage is established.

Symptoms

CLICK TO ENLARGE


Thyroid

The signs and symptoms of hypothyroidism vary widely, depending on the

severity of the hormone deficiency. But in general, any problems you do have tend to develop slowly, often over a number of years.

At first, you may barely notice the symptoms of hypothyroidism, such as fatigue and sluggishness, or you may simply attribute them to getting older. But as your metabolism continues to slow, you may develop more obvious signs and symptoms. Hypothyroidism symptom may include:

- Fatigue
- Sluggishness
- Increased sensitivity to cold
- Constipation
- Pale, dry skin
- A puffy face
- Hoarse voice
- An elevated blood cholesterol level
- Unexplained weight gain
- Muscle aches, tenderness and stiffness
- Pain, stiffness or swelling in your joints
- Muscle weakness
- Heavier than normal menstrual periods
- Brittle fingernails and hair
- Depression

When hypothyroidism isn't treated, signs and symptoms can gradually become more severe. Constant stimulation of your thyroid to release more hormones may lead to an enlarged thyroid (goiter). In addition, you may become more forgetful, your thought processes may slow or you may feel depressed.

Advanced hypothyroidism, known as myxedema, is rare, but when it occurs it can be life-threatening. Signs and symptoms include low blood pressure, decreased breathing, decreased body temperature, unresponsiveness and even coma. In extreme cases, myxedema can be fatal.

Hypothyroidism in children and teens

Although hypothyroidism most often affects middle-aged and older women, anyone can develop the condition, including infants and teenagers. Initially, babies born without a thyroid gland or with a gland that doesn't work properly may have few signs and symptoms. When newborns do have problems with hypothyroidism, they may include:

- Yellowing of the skin and whites of the eyes (jaundice). In most cases, this occurs when a baby's liver can't metabolize a molecule called bilirubin, which normally forms when the body recycles old or damaged red blood cells.
- Frequent choking.

- A large, protruding tongue.
- A puffy appearance to the face.

As the disease progresses, infants are likely to have trouble feeding and may fail to grow and develop normally. They may also have:

- Constipation
- Poor muscle tone
- Excessive sleepiness

When hypothyroidism in infants isn't treated, even mild cases can lead to severe physical and mental retardation.

In general, children and teens who develop hypothyroidism have the same signs and symptoms as adults do, but they may also experience:

- Poor growth, resulting in short stature
- Delayed development of permanent teeth
- Delayed puberty
- Poor mental development

Causes

Your thyroid is a small, butterfly-shaped gland located at the base of the front of your neck, just below your Adam's apple. Hormones produced by the thyroid gland have an enormous impact on your health, affecting all aspects of your metabolism.

As long as your thyroid releases the proper amounts of these hormones, your system functions normally. But sometimes your thyroid doesn't produce enough hormones, upsetting the balance of chemical reactions in your body. This condition is known as hypothyroidism.

Two main hormones
Your thyroid gland produces two main hormones, thyroxine (T-4) and triiodothyronine (T-3). They maintain the rate at which your body uses fats and carbohydrates, help control your body temperature, influence your heart rate and help regulate the production of protein. Your thyroid gland also produces calcitonin, a hormone that regulates the amount of calcium in your blood.

The rate at which thyroxine and triiodothyronine are released is controlled by your pituitary gland and your hypothalamus — an area at the base of your brain that acts as a thermostat for your whole system. The hypothalamus signals your pituitary gland to make a hormone called thyroid-stimulating hormone (TSH). Your pituitary gland then releases TSH — the amount depends on how much thyroxine and triiodothyronine are in your blood. Finally, your thyroid gland regulates its production of

hormones based on the amount of TSH it receives.

Although this process usually works well, the thyroid sometimes fails to produce enough hormones. Hypothyroidism may be due to a number of different factors, including:

- **Autoimmune disease (Hashimoto thyroiditis).** This is the most common cause of hypothyroidism. Autoimmune disorders occur when your immune system produces antibodies that attack your own tissues. Sometimes this process involves your thyroid gland. Scientists aren't sure why the body produces antibodies against itself. Some think a virus or bacteria might trigger the response, while others believe a genetic flaw may be involved. Most likely, autoimmune diseases result from more than one factor. But however it happens, these antibodies affect the thyroid's ability to produce hormones.
- **Treatment for hyperthyroidism.** People who produce too much thyroid hormone (hyperthyroidism) are often treated with radioactive iodine or anti-thyroid medications to reduce and normalize their thyroid function. However, in some cases, treatment of hyperthyroidism can result in permanent hypothyroidism.
- **Radiation therapy.** Radiation used to treat cancers of the head and neck can affect your thyroid gland and may lead to hypothyroidism.
- **Thyroid surgery.** Removing all or a large portion of your thyroid can diminish or halt hormone production. In that case, you'll need to take thyroid hormones for life.
- **Medications.** A number of medications can contribute to hypothyroidism. One such medication is lithium, which is used to treat certain psychiatric disorders. If you're taking medication, ask your doctor about its effect on your thyroid gland.

Less often, hypothyroidism may result from one of the following:

- **Congenital disease.** Approximately one in 3,000 babies in the United States is born with a defective thyroid gland or no thyroid gland at all. In most cases, the thyroid gland didn't develop normally for unknown reasons, but some children have an inherited form of the disorder. Often, infants with congenital hypothyroidism appear normal at birth. That's one reason why most states now require newborn thyroid screening.
- **Pituitary disorder.** A relatively rare cause of hypothyroidism is the failure of the pituitary gland to produce enough TSH — usually due to a benign tumor of the pituitary gland.
- **Pregnancy.** Some women develop hypothyroidism during or after pregnancy (postpartum hypothyroidism), often because they

produce antibodies to their own thyroid gland. Left untreated, hypothyroidism increases the risk of miscarriage, premature delivery and preeclampsia — a condition that causes a significant rise in a woman's blood pressure during the last three months of pregnancy. It can also seriously affect the developing fetus.

- **Iodine deficiency.** The trace mineral iodine — found primarily in seafood, seaweed, plants grown in iodine-rich soil and iodized salt — is essential for the production of thyroid hormones. In some parts of the world, iodine deficiency is common, but the addition of iodine to table salt has virtually eliminated this problem in the United States.

Risk factors

Although anyone can develop hypothyroidism, it occurs mainly in women older than 50, and the risk of developing the disorder increases with age. You also have an increased risk if you:

- Have a close relative, such as a parent or grandparent, with an autoimmune disease
- Have been treated with radioactive iodine or anti-thyroid medications
- Received radiation to your neck or upper chest
- Have had thyroid surgery (partial thyroidectomy)

When to seek medical advice

See your doctor if you're feeling tired for no reason or have any of the other signs or symptoms of hypothyroidism, such as dry skin, a pale, puffy face, constipation or a hoarse voice.

You'll also need to see your doctor for periodic testing of your thyroid function if you've had previous thyroid surgery, treatment with radioactive iodine or anti-thyroid medications, or radiation therapy to your head, neck or upper chest. However, it may take years or even decades before any of these therapies or procedures result in hypothyroidism.

If you have high blood cholesterol, talk to your doctor about whether hypothyroidism may be a cause. And if you're receiving hormone therapy for hypothyroidism, schedule follow-up visits as often as your doctor recommends. Initially, it's important to make sure you're receiving the correct dose of medicine. And over time, the dose you need to keep your thyroid functioning normally may change.

Tests and diagnosis

Because hypothyroidism is more prevalent in older women, some doctors

recommend that older women be screened for the disorder during routine annual physical examinations. Some doctors also recommend that pregnant women or women thinking about becoming pregnant be tested for hypothyroidism.

In general, your doctor may test for an underactive thyroid if you're feeling increasingly tired or sluggish, have dry skin, constipation and a hoarse voice, or have had previous thyroid problems or goiter.

Blood tests
Diagnosis of hypothyroidism is based on your symptoms and the results of blood tests that measure the level of TSH and sometimes the level of the thyroid hormone thyroxine. A low level of thyroxine and high level of TSH indicate an underactive thyroid. That's because your pituitary produces more TSH in an effort to stimulate your thyroid gland into producing more thyroid hormone.

In the past, doctors weren't able to detect hypothyroidism until symptoms were fairly advanced. But by using the sensitive TSH test, doctors are able to diagnose thyroid disorders much earlier — often before you ever experience symptoms. Because the TSH test is the best screening test, your doctor will likely check TSH first and follow with a thyroid hormone test if needed. TSH tests also play an important role in managing hypothyroidism. They help your doctor determine the right dosage of medication, both initially and over time.

In addition, TSH tests are used to help diagnose a condition called subclinical hypothyroidism, which usually causes no outward signs or symptoms. In this condition, you have normal blood levels of T-3 and T-4, but higher than normal levels of TSH.

Complications

Untreated hypothyroidism can lead to a number of health problems:

- **Goiter.** Constant stimulation of your thyroid to release more hormones may cause the gland to become larger — a condition known as goiter. Hashimoto thyroiditis is one of the most common causes of a goiter. Although generally not uncomfortable, a large goiter can affect your appearance and may interfere with swallowing or breathing.
- **Heart problems.** Hypothyroidism may also be associated with an increased risk of heart disease, primarily because high levels of low-density lipoprotein (LDL) cholesterol — the "bad" cholesterol — can occur in people with an underactive thyroid. Even subclinical hypothyroidism, a more benign condition than true hypothyroidism, can cause an increase in total cholesterol levels and impair the pumping ability of your heart. Hypothyroidism can also lead to an

enlarged heart and heart failure.

- **Mental health issues.** Depression may occur early in hypothyroidism and may become more severe over time. Hypothyroidism can also cause slowed mental functioning.
- **Myxedema.** This rare, life-threatening condition is the result of long-term, undiagnosed hypothyroidism. Its symptoms include intense cold intolerance and drowsiness followed by profound lethargy and unconsciousness. A myxedema coma may be triggered by sedatives, infection or other stress on your body. If you have symptoms of myxedema, you need immediate emergency medical treatment.
- **Infertility.** Low levels of thyroid hormone can interfere with ovulation, which impairs fertility. In addition, some of the causes of hypothyroidism — such as autoimmune disorder — also impair fertility. Treating hypothyroidism with thyroid hormone replacement therapy may not fully restore fertility. Other interventions may be needed, as well.
- **Birth defects.** Babies born to women with untreated thyroid disease may have a higher risk of birth defects than do babies born to healthy mothers. These children are more prone to serious intellectual and developmental problems.

  Infants with untreated hypothyroidism present at birth are also at risk of serious problems with both physical and mental development. But if the condition is diagnosed within the first few months of life, the chances of normal development are excellent.

Treatments and drugs

Standard treatment for hypothyroidism involves daily use of the synthetic thyroid hormone levothyroxine (Levothroid, Levoxyl, Synthroid, Unithroid). This oral medication restores adequate hormone levels, shifting your body back into normal gear.

One to two weeks after starting treatment, you'll notice that you're feeling less fatigued. The medication also gradually lowers cholesterol levels elevated by the disease and may reverse any weight gain. Treatment with levothyroxine is usually lifelong, but because the dosage you need may change, your doctor is likely to check your TSH level every year or so.

To determine the right dosage of levothyroxine initially, your doctor generally checks your level of TSH after two to three months. Excessive amounts of the hormone can cause side effects, such as increased appetite, insomnia, heart palpitations and shakiness.

If you have coronary artery disease or severe hypothyroidism, your doctor

may start treatment with a smaller amount of medication and gradually increase the dosage. Progressive hormone replacement allows your heart to adjust to the increase in metabolism.

Levothyroxine causes virtually no side effects when used in the appropriate dose and is relatively inexpensive. If you change brands, let your doctor know to ensure you're still receiving the right dosage. Also, don't skip doses or stop taking the drug because you're feeling better. If you do, the symptoms of hypothyroidism will gradually return.

Proper absorption of levothyroxine
Certain medications, supplements and even some foods may affect your ability to absorb levothyroxine. Talk to your doctor if you eat large amounts of soy products or a high-fiber diet or you take other medications, such as:

- Iron supplements
- Cholestyramine (Questran)
- Aluminum hydroxide, which is found in some antacids
- Calcium supplements

If you have subclinical hypothyroidism, discuss treatment with your doctor. For a relatively mild increase in TSH, you probably won't benefit from thyroid hormone therapy, and treatment could even be harmful. On the other hand, for a higher TSH level, thyroid hormones may improve your cholesterol level, the pumping ability of your heart or your energy level.

Alternative medicine

Although most doctors recommend synthetic thyroxine, natural extracts containing thyroid hormone derived from the thyroid glands of pigs are available. These products contain both thyroxine and triiodothyronine. Synthetic thyroid medications contain thyroxine only, and the triiodothyronine your body needs is derived from the thyroxine.

Extracts are available by prescription only and shouldn't be confused with the glandular concentrates sold in natural foods stores. These products aren't regulated by the Food and Drug Administration, and their potency isn't guaranteed.

By Mayo Clinic Staff
June 12, 2008

DS00353

Attachment F

AllThyroid.org

Ask the Doctor Homocysteine

Hypothyroidism and Homocysteine

"Is there any connection between hypothyroidism and homocysteine, as in 'The Homocysteine Revolution' by K. McCulley?" -- EB, NYC

Homocysteine is an amino acid (one of the building blocks of protein) which has recently been implicated as one of the risk factors for atherosclerosis, leading to heart attacks and strokes. While physicians have not yet reached a consensus, and few recommend screening of homocysteine levels (the way we screen cholesterol), recent studies support a a 3- to 4-fold increased risk of a heart attack among patients with the highest levels of homocysteine. Folate and vitamin B12, which are involved in the metabolism of homocysteine, may help reduce levels. It is not certain whether such treatment reduces the risk of heart attacks.

Preliminary studies have found that homocysteine levels are higher in patients with untreated hypothyroidism. Homocysteine levels were not lower in patients with hyperthyroidism.

Hypothyroidism is associated with an increased risk of atherosclerosis and heart disease. There has been debate as to whether this is due to increased cholesterol levels in hypothyroid patients, or whether there is a genetic linkage between Hashimoto's thyroiditis and atherosclerosis. It now appears possible that elevated homocysteine levels are another factor.

Treatment of hypothyroidism leads to a reduction in cholesterol, LDL cholesterol, and homocysteine levels, however, so patients taking appropriate doses of levothyroxine should not have to be more concerned than the average person about their homocysteine levels.

However, pernicious anemia is an autoimmune disorder resulting in vitamin B12 deficiency. Hashimoto's thyroiditis, which is the most common cause of hypothyroidism in developed countries, is also an autoimmune disorder. Therefore, patients with Hashimoto's thyroiditis should periodically have their vitamin B12 levels assessed to prevent vitamin B12 deficiency, which would, among other things, result in higher homocysteine levels.

The Thyroid Foundation Of America
One Longfellow Place, Suite 1518
Boston, MA 02114
(800) 832-8321

Attachment G

AllThyroid.org

Thyroid Disorders & Treatments : Treatments

Changing Your Thyroid Prescription

The Thyroid Foundation of America has become aware that the Food and Drug Administration has determined that different brands of thyroid hormone tablets are similar enough to make changes between brands or from brand to generic tablets appropriate. We do not agree.

Physicians evaluate the effectiveness of thyroid hormone treatment by measuring the serum TSH test. TSH stands for Thyroid Stimulating Hormone which is made in your pituitary gland and reflects the amount of active thyroid hormone in your system. If your thyroid hormone levels are too low, TSH will be high. If you have too much thyroid hormone, your TSH will be low or absent. Even slight changes in TSH level could signify a serious health risk. The problem is that most patients and many physicians may not be aware that a change in thyroid prescription may change the TSH and pose serious health risks.

Who is at risk?

If the thyroid hormone level rises above normal as a result of a medication change elderly individuals have an increased risk for osteoporosis and for heart rhythm problems, including atrial fibrillation which can cause heart attacks, strokes, or heart failure. Anyone with underlying heart disease could be at markedly increased risk for these complications. Patients with thyroid cancer are often given thyroid treatment to raise thyroid hormone levels above normal to suppress cancer cell growth. They too could have heart problems if new treatments further elevated their thyroid hormone levels.

Should the thyroid level fall as a result of a change in thyroid hormone medication, pregnant women who have been appropriately regulated on their previous medication could be at risk for hypothyroidism. Even mild degrees of hypothyroidism have been shown to increase a pregnant women's risk for miscarriage, a low birth weight baby, hypertension at the time of delivery, and a possible IQ deficit in their baby.

If Your Physician Changes Your Prescription

TFA recommends that you stay on whatever brand of thyroid hormone that your doctor prescribes. If your doctor does recommend a different thyroid medication for you, TFA recommends that you discuss with your doctor having a repeat TSH test in 4 to 6 weeks. If your TSH level is no longer normal, your doctor will advise you about an appropriate adjustment of your thyroid hormone dosage based on the results of your new TSH test. Six weeks after this adjustment, a final TSH test should be done to ensure stability and appropriate hormone levels. We note that it is likely that there will be a cost for such a change because of the need for extra office visits and extra TSH tests which may or may not be covered by your health insurance. We urge you to discuss these issues with your physician.

In some states, a pharmacist may make the recommendation for a change to a different brand or generic thyroid hormone. If so, discuss the changes with your physician who is better informed about your overall medical health and in the best position to make that decision.

We would also appreciate it if you would answer our TFA Thyroid Treatment Questionnaire giving us your experiences if you do change your medication.

If you have questions about this or other thyroid issues, please contact us by phone at 800-832-832.

The Thyroid Foundation Of America
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Attachment H

Medical Library

Printer-friendly format

American Association of Clinical Endocrinologists
The Voice of Clinical Endocrinology

Simple Tips for Patients With Thyroid Disorders

Know the Three "Ts" of Thyroid Therapy

1. **Think About Your Thyroid:** Know the symptoms of over- and underactive thyroid and talk to your doctor when you don't feel well. Look for bulges or protrusions in the neck, which may indicate the presence of a thyroid disorder.

2. **Take Your Medication:** Remember to be consistent. If you have been prescribed thyroid medication, take it at the same time every day, as directed by your doctor. Staying on the same brand and dose of thyroid medicine prescribed by your doctor is also critical for optimal disease management, so check your prescription at every refill to make sure it is correct.

3. **Track Your Condition:** Make sure your doctor checks your TSH (Thyroid Stimulating Hormone) and Free T4 levels regularly to make sure you are in the optimal range.

Target Your Numbers

TSH (thyroid-stimulating hormone) and Free T4 tests are simple blood tests that measure the appropriateness of the thyroid gland's hormone production. It is very important for patients with thyroid imbalance to know their TSH and Free T4 numbers.

- The optimal TSH range is 0.3 to 3.0 mIU/L.
- You should talk to your doctors about their Free T4 numbers since laboratory ranges can vary.

See an Endocrinologist

AACE recommends hypothyroid patients in the following categories to see an endocrinologist:

- Patients of age 18 years or less
- Patients with sub-optimal response to therapy
- Pregnant patients
- Cardiac patients
- Presence of goiter, nodule or other structural changes in the thyroid gland

the blood of normal people, similar to the range for height, and that a value of free T4 that is "within normal limits" for the general population may not be appropriate for a particular individual.

- Thyroid autoantibodies — indicates the likelihood of auto immune thyroiditis being the cause of hypothyroidism

A primary care physician may make the diagnosis of hypothyroidism, but assistance is often needed from an endocrinologist, a physician who is a specialist in thyroid diseases.

How Is Hypothyroidism Treated?

Hypothyroidism is treated with a single daily dose of levothyroxine, given as a tablet. An experienced physician can prescribe the correct form and dosage to return the thyroid balance to normal. Older patients who may have underlying heart disease are usually started at a low dose and gradually increased while younger healthy patients can be started on full replacement doses at once. Thyroid hormone acts very slowly in the body, so it may take several months after treatment is started to notice improvement in symptoms.

Since most cases of hypothyroidism are permanent and often progressive, it is necessary to treat this condition throughout one's lifetime. Periodic monitoring of TSH levels and clinical status are necessary to ensure that the proper dose is being given, since medication doses may have to be adjusted from time to time. Optimal adjustment of thyroid hormone dosage is critical, since the body is very sensitive to even small changes in thyroid hormone levels. The tablets come in over 10 different strengths, and it is essential to take them in a consistent manner every day. A dose of thyroid hormone that is too low may fail to prevent enlargement of the thyroid gland, allow symptoms of hypothyroidism to persist, and be associated with increased serum cholesterol levels, which may increase the risk for atherosclerosis and heart disease. A dose that is too high can cause symptoms of hyperthyroidism, create excessive strain on the heart, and lead to an increased risk of developing osteoporosis.

It is extremely important that women planning to become pregnant are kept well adjusted, since hypothyroidism can affect the development of the baby. During pregnancy, thyroid hormone replacement requirements often change, so more frequent monitoring is necessary. Various medications and supplements (particularly iron) may affect the absorption of thyroid hormone; therefore, the levels may need more frequent monitoring during illness or change in medication.

Thyroid hormone is critical for normal brain development in babies. Infants requiring thyroid hormone therapy should NOT be treated with purchased liquid suspensions, since the active hormone may deteriorate once dissolved and the baby could receive less thyroid hormone than necessary. Instead, infants with hypothyroidism should receive their thyroid hormone by crushing a single tablet daily of the correct dose and suspending it in one teaspoon of liquid.

Appropriate management of hypothyroidism requires continued care by a physician experienced in the treatment of this condition.

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EXHIBIT I

To: Counselor Staff
From: Treating Physician/Medical Staff/Mental Health
Re: Medical Notice Regarding I/M David Rush

To Whom It May Concern:

Please be advised that I/M David Rush (SBI #173418) of W-1, D-16 is a Chronic-care Patient who is (a) experiencing symptoms and/or (b) receiving treatments that are causing and/or likely to cause Rush to experience the following:

- Significant Mental Confusion or cognitive impairment,
- Significant Insomnia,
- Acute Depression,
- Significant Fatigue,
- Acute Irritation,
- Mood or Behavioral Problems, and
- Acute Flu-like symptoms and upset stomach.

This notice is provided as medical verification of the above so that interested Staff members will have access to this information for their consideration as Staff deems appropriate.

Thank you,

Lawrence L. McDonald MD — 8.2.08

Medical Staff/Mental Health Staff, (Ext _____) — Date

Symptoms of Treatment can persists for up to 3 months after the Treatment is stopped

L McDonald MD 8-2-08

C.C. Medical File,
W-1 Counselor Mrs. Pettyjohn
IBCC Classification Board
I/M David Rush

I/M: DAVID RUSH

SBI# 173418 UNIT W

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